THE PROGRESSIVE SCIENCE SERIES

EXPERIMENTS

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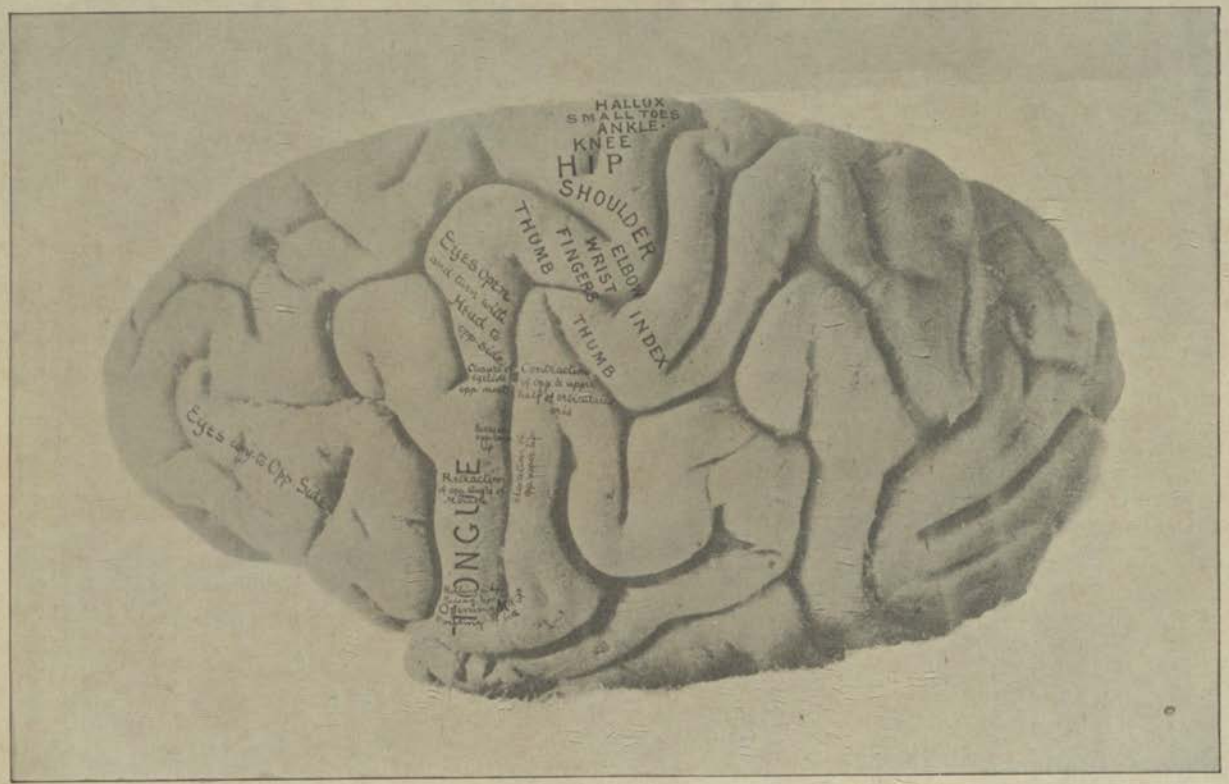
EXPERIMENTS ON ANIMALS



Brain of an Anthropoid Ape, showing the position of the Motor Centres.
(From a paper by Sir Victor Horsley and Dr Beevor. *Phil. Trans. Roy. Soc.*, 1892.)

Frontispiece

EXPERIMENTS ON ANIMALS

By STEPHEN PAGET

WITH AN INTRODUCTION BY
LORD LISTER

NEW AND REVISED EDITION

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TO

CHARLES ALFRED BALLANCE, M.S., F.R.C.S.

AND

WILLIAM HUNTER, M.D., F.R.C.P.

PREFACE

FOR twelve years it was the writer's business, as Secretary to the Association for the Advancement of Medicine by Research, to know something about experiments on animals, and to follow the working of the Act of 1876; and to give facts and references to a very large number of applicants. Believing that an account of these experiments, and of the conditions imposed upon them by the Act, might serve a useful purpose, he proposed to the Council of the Association that he should write a book on the subject. The Council accepted this proposal; and decided that the book should be written for general reading, that it should not be anonymous, and that it should be published without reserve.

It was of course a doubtful and embarrassing task. But, from twelve years' experience of the things that are said by the chief opponents of all experiments on animals, he knew that there was only one way of doing it—to give the original authorities, the plain facts, the very words, chapter and verse for everything.

Among those who kindly revised the proofs were Dr Rose Bradford and Prof. Starling, who

revised Part I.; Mr Shattock, who revised Part II.; and Prof. Schäfer. Certain valuable reports, references, and illustrations, were contributed by Mr R. H. Clarke, Mr Horsley, Dr Washbourn, Dr Beevor, and Surgeon-Major Ross.

1900.

THE name of Mr George Pernet was, by a stupid oversight, omitted from the above list. His careful researches into the history of the subject were of the utmost value.

In the present edition, some mistakes have been corrected, and some recent facts have been added. The first edition contained references to a few of the innumerable false statements that are made by the "Anti-vivisection" Societies. These references have now been deleted: for these Societies, quarrelling one with another, appealing for funds, and unable to show any real result for all the vast sums of money that have been wasted on them, are best left to themselves. They have no common policy, no appreciable influence either on the Home Office, or in Parliament, or on science, or on practice; and they are going the quickest way to lose their hold on the public attention. They have failed to accomplish anything important, either good or bad; and there is no need here to consider why they have failed.

1902.

INTRODUCTION TO THE FIRST EDITION

THIS work by Mr Paget is entirely a labour of love. Not being himself engaged in researches involving experiments upon the lower animals, he is not directly interested in the subject. But, in his official capacity as Secretary to the Association for the Advancement of Medicine by Research, he has become widely conversant with such investigations, and has been deeply impressed with the greatness of the benefits which they have conferred upon mankind, and the grievous mistake that is made by those who desire to suppress them.

The action of these well-meaning persons is based upon ignorance. They allow that man is permitted to inflict pain upon the lower animals when some substantial advantage is to be gained; but they deny that any good has ever resulted from the researches which they condemn.

How far such statements are from the truth will be evident to those who peruse this book. Its earlier pages deal with Physiology, the main basis of all sound medicine and surgery. The examples

given in this department are not numerous; they are, however, sufficiently striking, as indications that, from the discovery of the circulation of the blood onwards, our knowledge of healthy animal function has been mainly derived from experiments on animals.

The chief bulk of the work is devoted to the class of investigations which are most frequent at the present day; and it shows what a flood of light has been already thrown by Bacteriology upon the nature of human disease and the means of combating it.

The chapter on the Action of Drugs will be to many a startling disclosure of the gross ignorance that prevailed among physicians even in the earlier part of last century. The great revolution that has since taken place is no doubt largely due to advances in sciences other than Biology, especially Chemistry. But it could not have attained its present proportions without the ever-increasing knowledge of Physiology, based on experiments on animals; and Mr Paget shows how large a share these have had in the direct investigation of articles of the Materia Medica.

The concluding part of the volume discusses the restrictions which have been placed by the legislature in this country on those engaged in these researches, with the view of obviating possible abuse. Whether the Act in question has been really useful, whether it has not done more harm than good, by hampering and sometimes entirely

preventing legitimate and beneficent investigation, I will not now discuss.

Meanwhile I commend Mr Paget's book to the careful consideration of the reader.

LISTER.

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RAIN OF AN ANTHROPOID APE, showing the position of the Motor Centres . . . . . *frontispiece*

PART I

EXPERIMENTS IN PHYSIOLOGY

I

THE BLOOD

I.—Before Harvey

GALEN, born at Pergamos, 131 A.D., proved by experiments on animals that the brain is as warm as the heart, against the Aristotelian doctrine that the office of the brain is to keep the heart cool. He also proved that the arteries during life contain blood, not πνεῦμα, or the breath of life :—

"Ourselves, having tied the exposed arteries above and below, opened them between the ligatures, and showed that they were indeed full of blood."

Though all vessels bleed when they are wounded, yet this experiment was necessary to refute the fanciful teaching of Erasistratus and his followers, of whom Galen says .—

"Erasistratus is pleased to believe that an artery is a vessel containing the breath of life, and a vein is a vessel containing blood; and that

the vessels, dividing again and again, come at last to be so small that they can close their ultimate pores, and keep the blood controlled within them; yea, though the pores of the vein and of the artery lie side by side, yet the blood remains within its proper bounds, nowhere passing into the vessels of the breath of life. But when the blood is driven with violence from the veins into the arteries, forthwith there is disease; and the blood is poured the wrong way into the arteries, and there withstands and dashes itself against the breath of life coming from the heart, and turns the course of it — and this forsooth is fever."

For many centuries after Galen, men were content to worship his name and his doctrines, and forsook his method. They did not follow the way of experiment, and invented theories that were no help either in science or in practice. Here, in Galen's observation of living arteries, was a great opportunity for physiology; but the example that he set to those who came after him was forgotten by them, and, from the time of Galen to the time of the Renaissance, physiology remained almost where he had left it. Of the men of the Renaissance, Servetus, Cæsalpinus, Ruinius, and others, Harvey's near predecessors, this much only need be said here, that they did not discover the circulation of the blood; and that the claim made a few years ago to this discovery, on behalf of Cæsalpinus, by his countrymen, was not successful. But it is probable that Realdus (1516-1557) did understand the

passage of blood through the lungs, but not the general circulation. He says:—

"The blood is carried through the pulmonary artery to the lung, and there is attenuated; thence, mixed with air, it is carried through the pulmonary vein to the left ventricle of the heart: which thing no man hitherto has noted or left on record, though it is most worthy of the observation of all men. . . . And this is as true as truth itself; for if you will look, not only in the dead body but also in the living animal, you will always find this pulmonary vein full of blood, which assuredly it would not be if it were designed only for air and vapours. . . . Verily, I pray you, O candid reader, studious of authority, but more studious of truth, to make experiment on animals. You will find the pulmonary vein full of blood, not air or *fuligo*, as these men call it, God help them. Only there is no pulsation in the vein." (*De Re Anatomicâ*, Venice, 1559.)

Fabricius ab Aquapendente, Harvey's master at Padua, published his work on the valves of the veins—*De Venarum Ostiolis*—in 1603. He did not discover them. Sylvius speaks of them in his *Isagoge* (Venice, 1555), and they were known to Amatus (1552), and even to Theodoretus, Bishop of Syria, who lived, as John Hunter said of Sennertus, "the Lord knows how long ago." But Fabricius studied them most carefully; and in anatomy he left nothing more to be said about them. In physiology, his work was of little value; for he held that they were designed "to retard the blood in

some measure, lest it should run pell-mell into the feet, hands, and fingers, there to be impacted": they were to prevent distension of the veins, and to ensure the due nourishment of all parts of the body. It is true that he compared them to the locks or weirs of a river, but he understood neither the course nor the force of the blood: as Harvey said of him, "The man who discovered these valves did not understand their right use; neither did they who came after him"—*Harum valvularum usum rectum inventor non est assecutus, nec alii addiderunt; non est enim ne pondere deorsum sanguis in inferiora totus ruat; sunt namque in jugularibus deorsum spectantes, et sanguinem sursum ferri prohibentes.* Men had no idea of the rapidity and volume of the circulation; they thought of a sort of Stygian tide, oozing this way or that way in the vessels—Cæsalpinus was of opinion that it went one way in the daytime and another at night—nor did they see that the pulmonary circulation and the general circulation are one system, the same blood covering the whole course. The work that they did in anatomy was magnificent; Vesalius, and the other great anatomists of his time, are unsurpassed. But physiology had been hindered for ages by fantastic imaginings, and the facts of the circulation of the blood were almost as far from their interpretation in the sixteenth century as they had been in the time of Galen.

II.—Harvey (1578-1657).

The *De Motu Cordis et Sanguinis in Animalibus* was published at Frankfurt in 1628. And it begins with these words: *Cum multis vivorum dissectionibus, uti ad manum dabantur:—*

"When by many dissections of living animals, as they came to hand, I first gave myself to observing how I might discover with my own eyes, and not from books and the writings of other men, the use and purpose of the movement of the heart in animals, forthwith I found the matter hard indeed, and full of difficulty: so that I began to think, with Frascatorius, that the movement of the heart was known to God alone. For I could not distinguish aright either the nature of its systole and diastole, or when or where dilatation and contraction took place; and this because of the swiftness of the movement, which in many animals in the twinkling of an eye, like a flash of lightning, revealed itself to sight and then was gone; so that I came to believe that I saw systole and diastole now this way now the other, and movements now apart and now together. Wherefore my mind wavered; I had nothing assured to me, whether decided by me or taken from other men: and I did not wonder that Andreas Laurentius had written that the movement of the heart was what the ebb and flow of the Euripus had been to Aristotle.

"At last, having daily used greater disquisition and diligence, by frequent examination of many and various living animals—*multa frequenter et varia animalia viva introspiciendo*—and many observations put together, I came to believe that I had

succeeded, and had escaped and got out of this labyrinth, and therewith had discovered what I desired, the movement and use of the heart and the arteries. And from that time, not only to my friends, but also in public in my anatomical lectures, after the manner of the Academy, I did not fear to set forth my opinion in this matter."

It is plain, from Harvey's own words, that he gives to experiments on animals a foremost place among his methods of work. Take only the headings of his first four chapters :—

i. *Causæ, quibus ad scribendum auctor permotus fuerit.*
ii. *Ex vivorum dissectione, qualis fit cordis motus.*
iii. *Arteriarum motus qualis, ex vivorum dissectione.*
iv. *Motus cordis et auricularum qualis, ex vivorum dissectione.*

He thrusts it on us, he puts it in the foreground. Read the end of his Preface :—

"Therefore, from these and many more things of the kind, it is plain (since what has been said by men before me, of the movement and use of the heart and arteries, appears inconsistent or obscure or impossible when one carefully considers it) that we shall do well to look deeper into the matter; to observe the movements of the arteries and the heart, not only in man, but in all animals that have hearts; and by frequent dissection of living animals, and much use of our own eyes, to discern and investigate the truth—*vivorum dissectione frequenti, multâque autopsiâ, veritatem discernere et investigare.*"

Finally, take the famous passage in the eighth chapter, *De copiâ sanguinis transeuntis per cor e venis in arterias, et de circulari motu sanguinis*:—

"And now, as for the great quantity and forward movement of this blood on its way, when I shall have said what things remain to be said —though they are well worth considering, yet they are so new and strange that I not only fear harm from the envy of certain men, but am afraid lest I make all men my enemies; so does custom, or a doctrine once imbibed and fixed down by deep roots, like second nature, hold good among all men, and reverence for antiquity constrains them. Be that as it may, the die is cast now: my hope is in the love of truth, and the candour of learned minds. I bethought me how great was the quantity of this blood. Both from the dissection of living animals for the sake of experiment, with opening of the arteries, with observations manifold; and from the symmetry of the size of the ventricles, and of the vessels entering and leaving the heart—because Nature, doing nothing in vain, cannot in vain have given such size to these vessels above the rest—and from the harmonious and happy device of the valves and fibres, and all other fabric of the heart; and from many other things—when I had again and again carefully considered it all, and had turned it over in my mind many times—I mean the great quantity of the blood passing through, and the swiftness of its passage—and I did not see how the juices of the food in the stomach could help the veins from being emptied and drained dry, and the arteries contrariwise from being ruptured by the excessive flow of blood into them, unless blood were always

getting round from the arteries into the veins, and so back to the right ventricle—I began to think to myself whether the blood had a certain movement, as in a circle—*cœpi egomet mecum cogitare, an motionem quandam quasi in circulo haberet*—which afterward I found was true."

This vehement passage, which goes with a rush like that of the blood itself, is a good example of the width and depth of Harvey's work—how he used all methods that were open to him. He lived to fourscore years; "an old man," he says, "far advanced in years, and occupied with other cares": and, near the end of his life, he told the Hon. Robert Boyle that the arrangement of the valves of the veins had given him his first idea of the circulation of the blood:—

"I remember that when I asked our famous Harvey, in the only discourse I had with him, which was but a while before he died, what were the things which induced him to think of the circulation of the blood, he answered me that when he took notice that the valves in the veins of so many parts of the body were so placed that they gave free passage of the blood towards the heart, but opposed the passage of the venal blood the contrary way, he was invited to imagine that so provident a cause as Nature had not so placed so many valves without design; and no design seemed more probable than that, since the blood could not well, because of the interposing valves, be sent by the veins to the limbs, it should be sent by the arteries, and return through the veins, whose valves did not oppose its course that way."

But between this observation, which "invited him to imagine" a theory, and his final proofs of the circulation, lay a host of difficulties; and it is certain, from his own account of his work, that experiments on animals were of the utmost help to him in leading him "out of the labyrinth."

III.—After Harvey.

1. *The Capillaries.*

The capillary vessels were not known in Harvey's time: the *capillamenta* of Cæsalpinus were not the capillaries, but the νεῦρα of Aristotle. It was believed that the blood, between the smallest arteries and the smallest veins, made its way through "blind porosities" in the tissues, as water percolates through earth or through a sponge. The first account of the capillaries is in two letters (*De Pulmonibus*, 1661) from Malpighi, professor of medicine at Bologna, to Borelli, professor of mathematics at Pisa. In his first letter, Malpighi writes that he has tried in vain, by injecting the dead body, to discover how the blood passes from the arteries into the veins:—

"This enigma hitherto distracts my mind, though for its solution I have made many and many attempts, all in vain, with air and various coloured fluids. Having injected ink with a syringe into the pulmonary artery, I have again and again seen it escape (become extravasated into the tissues) at several points. The same thing happens with an injection of mercury.

These experiments do not give us the natural pathway of the blood."

But, in his second letter, he describes how he has examined, with a microscope of two lenses, the lung and the mesentery of a frog, and has seen the capillaries, and the blood in them:—

"Such is the divarication of these little vessels, coming off from the vein and the artery, that the order in which the vessel ramifies is no longer preserved, but it looks like a network woven from the offshoots of both vessels."

He was able, in a dead frog, to see the capillaries; and then, in a living frog, to see the blood moving in them. But, in spite of this work, it took nearly half a century before Harvey's teaching was believed by all men—*Tantum consuetudo apud omnes valet.*

2. *The Blood-pressure.*

Harvey had seen the facts of blood-pressure—*the great quantity of blood passing through, and the swiftness of its passage*—but he had not measured it. Keill's experiments on the blood-pressure (1718) were inexact, and of no value; and the first exact measurements were made by Stephen Hales, who was rector of Farringdon, Hampshire, and minister of Teddington, Middlesex; a Doctor of Divinity, and a Fellow of the Royal Society. His experiments, in their width and diversity, were not surpassed even by those of John Hunter, and were extended far over physiology, vegetable physiology,

organic and inorganic chemistry, and physics; they ranged from the invention of a sea-gauge to the study of solvents for the stone, and he seems to have experimented on every force in Nature. The titles of his two volumes of *Statical Essays* (1726-1733) show the great extent of his non-clerical work:—

Volume I. *Statical Essays, containing Vegetable Statics, or an Account of some Statical Experiments on the Sap in Vegetables, being an Essay towards a Natural History of Vegetation; also, a Specimen of an Attempt to Analyse the Air, by a great Variety of Chymio-Statical Experiments.*

Volume II. *Statical Essays, containing Hæmostatics, or an Account of some Hydraulic and Hydrostatical Experiments made on the Blood and Blood-vessels of Animals; also, an Account of some Experiments on Stones in the Kidneys and Bladder, with an Enquiry into the Nature of those anomalous Concretions.*

"We can never want matter for new experiments," he says in his preface. "We are as yet got little further than to the surface of things: we must be content, in this our infant state of knowledge, while we know in part only, to imitate children, who, for want of better skill and abilities, and of more proper materials, amuse themselves with slight buildings. The farther advances we make in the knowledge of Nature, the more probable and the nearer to truth will our conjectures approach: so that succeeding generations, who shall have the benefit and advantage both of

their own observations and those of preceding generations, may then make considerable advances, when *many shall run to and fro, and knowledge shall be increased.*"

His account of his plan of measuring the blood-pressure, and of one of many experiments that he made on it, is as follows :—

"Finding but little satisfaction in what had been attempted on this subject by Borellus and others, I endeavoured, about twenty-five years since, by proper experiments, to find what was the real force of the blood in the crural arteries of dogs, and about six years afterwards I repeated the like experiments on two horses, and a fallow doe ; but did not then pursue the matter any further, being discouraged by the disagreeableness of anatomical dissections. But having of late years found by experience the advantage of making use of the statical way of investigation, not only in our researches into the nature of vegetables, but also in the chymical analysis of the air, I was induced to hope for some success, if the same method of enquiry were applied to animal bodies. . . .

"Having laid open the left crural artery (of a mare), I inserted into it a brass pipe whose bore was $\frac{1}{6}$ of an inch in diameter ; and to that, by means of another brass pipe which was fitly adapted to it, I fixed a glass tube of nearly the same diameter, which was 9 feet in length ; then, untying the ligature on the artery, the blood rose in the tube 8 feet 3 inches perpendicular above the level of the left ventricle of the heart, but it did not attain to its full height at once : it rushed up gradually at each pulse 12, 8, 6, 4, 2, and sometimes 1 inch.

When it was at its full height, it would rise and fall at and after each pulse 2, 3, or 4 inches, and sometimes it would fall 12 or 14 inches, and have there for a time the same vibrations up and down, at and after each pulse, as it had when it was at its full height, to which it would rise again, after forty or fifty pulses."

3. *The Collateral Circulation.*

After Hales, came John Hunter, who was five years old when the *Statical Essays* were published. His experiments on the blood were mostly concerned with its properties, not with its course; but one great experiment must be noted here that puts him in line with Harvey, Malpighi, and Hales. He got from it his knowledge of the collateral circulation; he learned how the obstruction of an artery is followed by enlargement of the vessels in its neighbourhood, so that the parts beyond the obstruction do not suffer from want of blood: and the facts of collateral circulation were fresh in his mind when, a few months later, he conceived and performed his operation for aneurysm (December, 1785). The "old operation" gave him no help here; and "Anel's operation" was but a single instance, and no sure guide for Hunter, because Anel's patient had a different sort of aneurysm. Hunter knew that the collateral circulation could be trusted to nourish the limb, if the femoral artery were ligatured in "Hunter's canal" for the cure of popliteal aneurysm; and he got this knowledge from the experiment that he had made on one of the deer

in Richmond Park, to see the influence of ligature of the carotid artery on the growth of the antler. The following account of this experiment was given by Sir Richard Owen, who had it from Mr Clift, Hunter's devoted pupil and friend:—

"In the month of July, when the bucks' antlers were half-grown, he caused one of them to be caught and thrown; and, knowing the arterial supply to the hot 'velvet,' as the keepers call it, Hunter cut down upon and tied the external carotid; upon which, laying his hand upon the antler, he found that the pulsations of the arterial channels stopped, and the surface soon grew cold. The buck was released, and Hunter speculated on the result—whether the antler, arrested at mid-growth, would be shed like the full-grown one, or be longer retained. A week or so afterward he drove down again to the park, and caused the buck to be caught and thrown. The wound was healed about the ligature; but on laying his hand on the antler, he found to his surprise that the warmth had returned, and the channels of supply to the velvety formative covering were again pulsating. His first impression was that his operation had been defective. To test this, he had the buck killed and sent to Leicester Square. The arterial system was injected. Hunter found that the external carotid had been duly tied. But certain small branches, coming off on the proximal or heart's side of the ligature, had enlarged; and, tracing-on these, he found that they had anastomosed with other small branches from the distal continuation of the carotid, and these new channels had restored the supply to the growing antler. . . . Here was a consequence of his experiment he had not at all fore-

seen or expected. A new property of the living arteries was unfolded to him."

All the anatomists had overlooked this physiological change in the living body, brought about by disease. And the surgeons, since anatomy could not help them, had been driven by the mortality of the "old operation" to the practice of amputation.

4. *The Mercurial Manometer.*

Hale's experiments on the blood-pressure were admirable in their time; but neither he nor his successors could take into account all the physiological and mathematical facts of the case. But a great advance was made in 1828, when Poiseuille published his thesis, *Sur la Force du Cœur Aortique*, with a description of the mercurial manometer. Poiseuille had begun with the received idea that the blood-pressure in the arteries would vary according to the distance from the heart, but he found by experiment that this doctrine was wrong:—

"At my first experiments, wishing to make sure whether the opinions, given *à priori*, were true, I observed to my great astonishment that two tubes, applied at the same time to two arteries at different distances from the heart, gave columns of exactly the same height, and not, as I had expected, of different heights. This made the work very much simpler, because, to whatever artery I applied the instrument, I obtained the same results that I should have got by placing it on the ascending aorta itself."

The following account of his manometer, and the picture of it, are given in his thesis:—

"Take a glass tube, having a horizontal arm AB, a vertical descending arm BC, and a third ascending arm DE, and curved to a quarter of a circle at B, and to half a circle at CD. Suppose that we put mercury in the part GCDH, the tube being vertical, the levels G and H of the mercury will be the same in the two arms. If the blood be passed into ABG through the orifice A, connected with an artery, it will press on the surface of the mercury at G: the metal will be pressed down in the arm BC from G to K, for example, when it will rise in the arm DE to I. It is evident, from the laws of hydrostatics, that the total force with which the blood moves in the artery will be measured by the weight of a cylinder of mercury, whose base is a circle of the diameter of the artery, and whose height is the difference IK between the two levels of the mercury; deduction being made, of course, of the height of the little column of mercury balancing the column of blood BK."

He found also, by experiments, that the coagulation of the blood in the tube could be prevented by filling the part ABG of the tube with a saturated solution of sodium carbonate. The tube, thus prepared, was connected with the artery by a fine cannula, exactly fitting the artery. With this instrument, Poiseuille was able to obtain results far more accurate than those of Hales, and to observe the diverse influences of the respiratory movements on the blood-pressure. He sums up his results in these words:—

"I come to this irrevocable conclusion, that the force with which a molecule of blood moves, whether in the carotid, or in the aorta, etc., is exactly equal to the force which moves a molecule in the smallest arterial branch; or, in other words, that a molecule of blood moves with the same force over the whole course of the arterial system—which, *à priori*, with all the physiologists, I was far from thinking."

And he adds, in a foot-note :—

"When I say that this force is the same over the whole course of the arterial system, I do not mean to deny that it must needs be modified at certain points of this system, which present a special arrangement, such as the anastomosing arches of the mesentery, the arterial circle of Willis, etc."

Later, in 1835, he published a very valuable memoir on the movement of the blood in the capillaries under different conditions of heat, cold, and atmospheric pressure.

5. *The Registration of the Blood-pressure.*

Poiseuille's work, in its turn, was left behind as physiology went forward: especially, the discovery of the vaso-motor nerves compelled physiologists to reconsider the whole subject of the blood-pressure. If Poiseuille's thesis (1828) be compared with Marey's book (1863), *Physiologie Médicale de la Circulation du Sang*, it will be evident at once how much wider and deeper the problem had become. Poiseuille's thesis is chiefly concerned with mathematics and hydrostatics; it suggests

no method of immediate permanent registration of the pulse, and is of no great value to practical medicine: Marey's book, by its very title, shows what a long advance had been made between 1828 and 1863—*Physiologie Médicale de la Circulation du Sang, basée sur l'étude graphique des mouvements du cœur et du pouls artériel, avec application aux maladies de l'appareil circulatoire.* Though the contrast is great between Hales' may-pole and Poiseuille's manometer, there is even a greater contrast between Poiseuille's mathematical calculations and Marey's practical use of the sphygmograph for the study of the blood-pressure in health and disease. Marey had the happiness of seeing medicine, physiology, and physics, all three of them working to one end:—

"La circulation du sang est un des sujets pour lesquels la médecine a le plus besoin de s'éclairer de la physiologie, et où celle-ci à son tour tire le plus de lumière des sciences physiques. Ces dernières années sont marquées par deux grands progrès qui ouvrent aux recherches à venir des horizons nouveaux: en Allemagne, l'introduction des procédés graphiques dans l'étude du mouvement du sang; en France, la démonstration de l'influence du système nerveux sur la circulation périphérique. Cette dernière découverte, que nous devons à M. Cl. Bernard, et qui depuis dix ans a donné tant d'impulsion à la science, montre mieux que toute autre combien la physiologie est indispensable à la médecine, tandis que les travaux allemands ont bien fait ressortir l'importance des connaissances physiques dans les études médicales."

Marey's sphygmograph was not the first instrument of its kind. There had been, before it, Hérisson's sphygmometer, Ludwig's kymographion, and the sphygmographs of Volckmann, King, and Vierordt. But, if one compares a Vierordt tracing with a Marey tracing, it will be plain that Marey's results were far advanced beyond the useless "oscillations isochrones" recorded by Vierordt's instrument.

Beside this improved sphygmograph, Chauveau and Marey also invented the cardiograph, for the observation of the blood-pressure within the cavities of the heart. Their cardiograph was a set of very delicate elastic tambours, resting on the heart, or passed through fine tubes into the cavities of the heart,* and communicating impulses to levers with writing-points. These writing-points, touching a revolving cylinder, recorded the variations of the endocardial pressure, and the duration of the auricular and ventricular contractions.

It is impossible here to describe the subsequent study of those more abstruse problems that the older physiologists had not so much as thought of:

* "On peut s'assurer de l'innocuité de ce premier temps de l'expérience en examinant l'animal, qui n'est nullement troublé, qui marche et mange comme de coutume. En comptant le chiffre du pouls, ou trouve quelquefois une légère accéleration, surtout dans les premiers instants ; mais les mouvements du cœur sont toujours réguliers, et donnent, à l'auscultation, des bruits d'un caractère normal." (Marey, *loc. cit.* p. 63.)

the minutest variations of the blood-pressure, the multiple influences of the nervous system on the heart and blood-vessels, the relations between blood-pressure and secretion, the automatism of the heart-beat, the influence of gravitation, and other finer and more complex issues of physiology. But, even if one stops at Marey's book, now forty years old, there is an abundant record of good work, from the discovery of the circulation to the invention of the sphygmograph.

II

THE LACTEALS

ASELLIUS, in his account of his discovery of the lacteal vessels (1622), is of opinion that certain of "the ancients" had seen these vessels, but had not recognised them. He has a great reverence for authority: Hippocrates, Plato, Aristotle, the Stoics, Herophilus, Galen, Pollux, Rhases, and a host of other names, he quotes them all, and all with profound respect; and comes to this conclusion: "It did not escape the ancients, that certain vessels must needs be concerned with containing and carrying the chyle, and certain other vessels with the blood: but the true and very vessels of the chyle, that is, my 'veins,' though they were seen by some of the ancients, yet they were recognised by none of them." He can forgive them all, except Galen, *qui videtur nosse omnino debuisse*—"but, as for Galen, I know not at all what I am to think. For he, who made more than six hundred sections of living animals, as he boasts himself, and so often opened many animals when they were lately fed, are we to think it possible that these veins never showed themselves to him, that he never had them under his eyes,

that he never investigated them—he to whom Erasistratus had given so great cause for searching out the whole matter?" Probably, the milk-white threads had been taken for nerves by those who had seen them: and those who had never seen them, but believed in their existence, rested their belief on a general idea that the chyle must, somehow, have vessels of its own apart from the blood-vessels. What Galen and Erasistratus must have seen, Asellius and Pecquet discovered: and Harvey gives a careful review of the discovery in his letters to Nardi (May 1652) and to Morison (November 1653). He does not accept it; but the point is that he recognises it as a new thing altogether.

A year or two after he had made the discovery, Asellius died; and his work was published in 1627 by two Milanese physicians, and was dedicated by them to the senate of the Academy of Milan, where Asellius had been professor of anatomy. The full title of his book is, *De Lactibus sive Lacteis Venis, quarto Vasorum Mesaraicorum genere novo invento, Gasparis Asellii Cremonensis, Anatomici Ticinensis, Dissertatio. Quâ sententiæ anatomicæ multæ vel perperam receptæ convelluntur vel partim perceptæ illustrantur.* He gives the following account of the discovery, in the chapter entitled *Historia primæ vasorum istorum inventionis cum fide narrata.* On 23rd July 1622, demonstrating the movement of the diaphragm in a dog, he observed suddenly, "as it were, many threads, very thin and very white, dispersed through the whole mesentery and through the intestines, with ramifications almost endless"—

plurimos, eosque tenuissimos candidosissimosque ceu funiculos per omne mesenterium et per intestina infinitis propemodum propaginibus dispersos:—

"Thinking at first sight that they were nerves, I did not greatly heed them. But soon I saw that I was wrong, for I bethought me that the nerves, which belong to the intestines, are distinct from these threads, and very different from them, and have a separate course. Wherefore, struck by the newness of the matter, I stopped for a time silent, while one way and another there came to my mind the controversies that occupy anatomists, as to the mesenteric veins and their use; which controversies are as full of quarrels as of words. When I had pulled myself together, to make experiment, taking a very sharp scalpel, I pierce one of the larger threads. Scarcely had I hit it off, when I see a white fluid running out, like milk or cream. At which sight, when I could not hold my joy, turning to those who were there, first to Alexander Tadinus and Senator Septalius, both of them members of the most honourable College of Physicians, and, at the time of this writing, officers of the public health, '*I have found it*,' I say like Archimedes; and therewith invite them to the so pleasant sight of a thing so unwonted; they being agitated, like myself, by the newness of it."

He then describes the collapse and disappearance of the vessels at death, and the many experiments which he made for further study of them; and the failure, when he tried to find them in animals not lately fed. He did not trace them beyond the mesentery, and believed that they

emptied themselves into the liver. The discovery of their connection with the receptaculum chyli and the thoracic duct was made by Jehan Pecquet of Dieppe, Madame de Sévigné's doctor, her "good little Pecquet." The full title of his book (2nd ed., 1654) is, *Experimenta Nova Anatomica, quibus incognitum hactenus Receptaculum, et ab eo per Thoracem in ramos usque subclavios Vasa Lactea deteguntur.* He has not the academical learning of Asellius, nor his obsequious regard for the ancients; and the discovery of the thoracic duct came, as it were by chance, out of an experiment that was of itself wholly useless. He had killed an animal by removing its heart, and then saw a small quantity of milky fluid coming from the cut end of the vena cava—*Albicantem subinde Lactei liquoris, nec certe parum fluidi scaturiginem, intra Venæ Cavæ fistulam, circā dextri sedem Ventriculi, miror effluere* —and found that this fluid was identical with the chyle in the lacteals. In another experiment, he succeeded in finding the thoracic duct—"At last, by careful examination deep down along the sides of the dorsal vertebræ, a sort of whiteness, as of a lacteal vessel, catches my eyes. It lay in a sinuous course, close up against the spine. I was in doubt, for all my scrutiny, whether I had to do with a nerve or with a vessel. Therefore, I put a ligature a little below the clavicular veins; and then the flaccidity above the ligature, and the swelling of the distended duct below the ligature, broke down my doubt—*Ergo subducto paulo infra Claviculas vinculo, cum a ligaturâ sursum flaccesceret, superstite deorsum*

turgentis alveoli tumore, dubium meum penitus enervavit. . . . Laxatis vinculis, lacteus utrinque rivulus in Cavam affatim Chylum profudit."

It is to be noted that Asellius and Pecquet, both of them, made their discoveries as it were by chance. Unless digestion were going on, the lacteals would be empty and invisible; and, on the dead body, lacteals, receptaculum, and thoracic duct would all be empty. For these reasons, it cost a vast number of experiments to prove the existence, and to discover the course, of these vessels. Once found in living animals, they could be injected and dissected in the dead body; but they had been overlooked by Vesalius and the men of his time.

From the discovery of the lacteals came the discovery of the whole lymphatic system. Daremberg, in his *Histoire des Sciences Médicales* (Paris, 1870), after an account of Pecquet's work, says:—

"Up to this point, we have seen English, Italians, and French working together, with more or less success and genius, to trace the true ways of blood and chyle: there is yet one field of work to open up, the lymphatics of the body. The chief honour here belongs, without doubt, to the Swede Rudbeck, though the Dane Bartholin has disputed it with him, with equal acrimony and injustice."

Rudbeck's work (1651-54) coincides exactly, in point of time, with the first and second editions, 1651 and 1654, of Pecquet's *De Lactibus*. It may be said, therefore, that the whole doctrine of the lymphatic system was roughed out halfway through the seventeenth century.

III

THE GASTRIC JUICE

FROM many causes, the experimental study of the digestive processes came later than the study of the circulation. As an object of speculative thought, digestion was a lower phase of life, the work of crass spirits, less noble than the blood; from the point of view of science, it could not be studied ahead of organic chemistry, and got no help from any other sort of knowledge; and, from the medical point of view, it was the final result of many unknown internal forces that could not be observed or estimated either in life or after death. It did not, like the circulation, centre itself round one problem; it could not be focussed by the work of one man. For these reasons, and especially because of its absolute dependence on chemistry for the interpretation of its facts, it had to bide its time; and Réaumur's experiments are separated from the publication of Harvey's *De Motu Cordis et Sanguinis* by a hundred and thirty years.

The following account of the first experiments on digestion is taken from Claude Bernard's *Physiologie Opératoire*, 1879:—

"The true experimental study of digestion is of comparatively recent date; the ancients were content to find comparisons, more or less happy, with common facts. Thus, for Hippocrates, digestion was a 'coction': for Galen, a 'fermentation,' as of wine in a vat. In later times, van Helmont started this comparison again: for him, digestion was a fermentation like that of bread: as the baker, having kneaded the bread, keeps a little of the dough to leaven the next lot kneaded, so, said van Helmont, the intestinal canal never completely empties itself, and the residue that it keeps after each digestion becomes the leaven that shall serve for the next digestion.

"The first experimental studies on the digestion date from the end of the seventeenth century, when the Academy of Florence was the scene of a famous and long controversy between Borelli and Valisnieri. The former saw nothing more in digestion than a purely mechanical act, a work of attrition whereby the ingesta were finely divided and as it were pulverised: and in support of this opinion Borelli invoked the facts that he had observed relating to the gizzard of birds. We know that this sac, with its very thick muscular walls, can exercise on its contents pressure enough to break the hardest bodies. Identifying the human stomach with the bird's gizzard, Borelli was led to attribute to the walls of the stomach an enormous force, estimated at more than a thousand pounds; whose action, he said, was the very essence of digestion. Valisnieri, on the contrary, having had occasion to open the stomach of an ostrich, had found there a fluid which seemed to act on bodies immersed in it; this fluid, he said, was the active agent of digestion, a kind of *aqua fortis* that dissolved food.

"These two opposed views, resulting rather from observations than from regularly instituted experiments, were the starting-point of the experimental researches undertaken by Réaumur in 1752. To resolve the problem set by Borelli and Valisnieri, Réaumur made birds swallow food enclosed in fenestrated tubes, so that the food, protected from the mechanical action of the walls of the stomach, was yet exposed to the action of the gastric fluid. The first tubes used (glass, tin, etc.) were crushed, bent, or flattened by the action of the walls of the gizzard; and Réaumur failed to oppose to this force a sufficient resistance, till he employed leaden tubes thick enough not to be flattened by a pressure of 484 pounds: which was, in fact, the force exercised by the contractile walls of the gizzard in turkeys, ducks, and fowls under observation. These leaden tubes—filled with ordinary grain, and closed only by a netting that let pass the gastric juices—these tubes, after a long stay in the stomach, still enclosed grain wholly intact, unless it had been crushed before the experiment. When they were filled with meat, it was found changed, but not digested. Réaumur was thus led at first to consider digestion, in the gallinaceæ, as pure and simple trituration. But, repeating these experiments on birds of prey, he observed that digestion in them consists essentially in dissolution, without any especial mechanical action, and that it is the same with the digestion of meat in all animals with membranous stomachs. To procure this dissolving fluid, Réaumur made the birds swallow sponges with threads attached: withdrawing these sponges after a definite period, he squeezed the fluid into a glass, and tested its action on meat. That was the first attempt at

artificial digestion *in vitro*. He did not carry these last investigations very far, and did not obtain very decisive results; nevertheless he must be considered as the discoverer of artificial digestion."

After Réaumur, the Abbé Spallanzani (1783) made similar observations on many other animals, including carnivora. He showed that even in the gallinaceæ there was dissolution of food, not mere trituration: and observed how after death the gastric fluid may under certain conditions act on the walls of the stomach itself.

"Henceforth the experimental method had cut the knot of the question raised by the theories of Borelli and Valisnieri: digestion could no longer be accounted anything but a dissolution of food by the fluid of the stomach, the gastric juice. But men had still to understand this gastric juice, and to determine its nature and mode of action. Nothing could be more contradictory than the views on this matter. Chaussier and Dumas, of Montpellier, regarded the gastric juice as of very variable composition, one time alkaline, another acid, according to the food ingested. Side by side with these wholly theoretical opinions, certain results of experiments had led to ideas just as erroneous, for want of rigorous criticism of methods; it was thus that Montègre denied the existence of the gastric juice as a special fluid; what men took for gastric juice, he said, was nothing but the saliva turned acid in the stomach. To prove his point, he made the following experiment:—He masticated a bit of bread, then put it

out on a plate; it was at first alkaline, then at the end of some time it became acid. In those days (1813) this experiment was a real embarrassment to the men who believed in the existence of a special gastric juice: we have now no need to refute it.

"These few instances suffice to show how the physiologists were unsettled as to the nature and properties of the gastric juice. Then (1823) the Academy had the happy idea of proposing digestion as a subject for a prize. Tiedemann and Gmelin in Germany, Leuret and Lassaigne in France, submitted works of equal merit, and the Academy divided the prize between them. The work of Tiedemann and Gmelin is of especial interest to us on account of the great number of their experiments, from which came not only the absolute proof of the existence of the gastric juice, but also the study of the transformation of starch into glucose. Thus the theory of digestion entered a new phase: it was finally recognised, at least for certain substances, that digestion is not simply dissolution, but a true chemical transformation." (Cl. Bernard, *loc. cit.*)

In 1825 Dr William Beaumont, a surgeon in the United States Army, began his famous experiments on Alexis St Martin, a young Canadian travelling for the American Fur Company, who was shot in the abdomen on 6th June 1822, and recovered, but was left with a permanent opening in his stomach. Since the surgery of those days did not favour an operation to close this fistula, Dr Beaumont took St Martin into his service, and between 1825 and 1833 made a vast number of

experiments on him. These he published,* and they were of great value. But it is to be noted that the ground had been cleared already, fifty years before, by Réaumur and Spallanzani:—

"*I make no claim to originality in my opinions*, as it respects the existence and operation of the gastric juice. My experiments confirm the doctrines (with some modifications) taught by Spallanzani, and many of the most enlightened physiological writers." (Preface to Dr Beaumont's book.)

Further, it is to be noted that Alexis St Martin's case proves that a gastric fistula is not painful. Scores of experiments were made on him, off and on, for nine years:—

"During the whole of these periods, from the spring of 1824 to the present time (1833), he has enjoyed general good health, and perhaps suffered much less predisposition to disease than is common to men of his age and circumstances in life. He has been active, athletic, and vigorous; exercising, eating, and drinking like other healthy and active people. For the last four months he has been unusually plethoric and robust, though constantly subjected to a continuous series of experiments on the interior of the stomach; allowing to be introduced or taken out at the aperture different kinds of food, drinks, elastic catheters, thermometer tubes, gastric juice, chyme, etc., almost daily, and sometimes hourly.

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* *Experiments and Observations on the Gastric Juice, and the Physiology of Digestion*, by William Beaumont, M.D.; Edinburgh, 1838.

"Such have been this man's condition and circumstances for several years past; and he now enjoys the most perfect health and constitutional soundness, with every function of the system in full force and vigour." (Dr Beaumont, *loc. cit.* p. 20.)

In 1834 Eberlé published a series of observations on the extraction of gastric juice from the mucous membrane of the stomach after death; in 1842 Blondlot of Nancy studied the gastric juice of animals by the method of a fistula, such as Alexis St Martin had offered for Dr Beaumont's observation. After Blondlot, came experiments on the movements of the stomach, and on the manifold influences of the nervous system on digestion.

It has been said, times past number, that an animal with a fistula is in pain. It is not true. The case of St Martin is but one out of a multitude of these cases: an artificial orifice of this kind is not painful.

IV

GLYCOGEN

CLAUDE BERNARD'S discovery of glycogen in the liver had a profound influence both on physiology and on pathology. Take first its influence on pathology. Diabetes was known to Celsus, Aretæus, and Galen; Willis, in 1674, and Morton, in 1675, noted the distinctive sweetness of the urine; and their successors proved the presence of sugar in it. Rollo, in 1787, observed that vegetable food was bad for diabetic patients, and introduced the strict use of a meat diet. But Galen had believed that diabetes was a disease of the kidneys, and most men still followed him: nor did Rollo greatly advance pathology by following not Galen, but Aretæus. Later, with the development of organic chemistry, came the work of Chevreuil (1815), Tiedemann and Gmelin (1823), and other illustrious chemists: and the pathology of diabetes grew more and more difficult:—

"These observations gave rise to two theories: the one, that sugar is formed with abnormal rapidity in the intestine, absorbed into the blood, and

excreted in the urine; the other, that diabetes is due to imperfect destruction of the sugar, either in the intestine or in the blood. Some held that it underwent conversion into lactic acid as it was passing through the intestinal walls, while others believed it to be destroyed in the blood by means of the alkali therein contained."*

Thus, before Claude Bernard (1813-1878), the pathology of diabetes was almost worthless. And, in physiology, his work was hardly less important than the work of Harvey. A full account of it, in all its bearings, is given in Sir Michael Foster's *Life of Claude Bernard* (Fisher Unwin, 1899).

In Bernard's *Leçons sur le Diabète et la Glycogenèse Animale* (Paris, 1877), there is a sentence that has been misquoted many times:—

Sans doute, nos mains sont vides aujourd'hui, mais notre bouche peut être pleine de légitimes promesses pour l'avenir.

This sentence has been worked so hard that some of the words have got rubbed off it: and the statement generally made is of this kind:—

Claude Bernard himself confessed that his hands were empty, but his mouth was full of promises.

Of course, he did not mean that he was wrong in his facts. But, in this particular lecture, he is speaking of the want of more science in practice,

* *Reynolds' System of Medicine*, vol. v., art. "Diabetes Mellitus."

looking forward to a time when treatment should be based on science, not on tradition. Medicine, he says, is neither science nor art. Not science—*Trouverait-on aujourd'hui un seul médecin raisonnable et instruit osant dire qu'il prévoit d'une manière certaine la marche et l'issue d'une maladie ou l'effet d'une remède?* Not art, because art has always something to show for its trouble: a statue, a picture, a poem—*Le médecin artiste ne crée rien, et ne laisse aucune œuvre d'art, à moins d'appliquer ce titre à la guérison du malade. Mais quand le malade meurt, est-ce également son œuvre? Et quand il guérit, peut-il distinguer sa part de celle de la nature?*

To Claude Bernard, experiments on animals for the direct advancement of medicine seemed a new thing: new, at all events, in comparison with the methods of some men of his time. He was only saying what a great English physiologist said in 1875 to the Royal Commission:—

It is my profound conviction that a future will come, it may be a somewhat distant future, in which the treatment of disease will be really guided by science. Just as completely as mechanical science has come to be the guide of the mechanical arts, do I believe, and I feel confident, that physiological science will eventually come to be the guide of medicine and surgery.

Anyhow, lecturing a quarter of a century ago on diabetes, his special subject, Claude Bernard spoke out his longing to compel men into the ways of

science, to give them some immediate sign which they could not refuse to see:—

"At this present time, medicine is passing from one period to another. The old traditions are losing ground, and scientific medicine (*la médecine expérimentale*) has got hold of all our younger men: every day it gains ground, and will establish itself against all its critics, and in spite of the excesses of those who are over-zealous for its honour. . . . And when men ask us what are the results of scientific medicine, we are driven to answer that it is scarcely born, that it is still in the making. Those who care for nothing but an immediate practical application must remember Franklin's words, *What is the use of a new-born child, but to become a man?* If you deliberately reject scientific medicine, you fail to see the natural development of man's mind in all the sciences. Without doubt, our hands are empty to-day, but our mouth may well be filled with legitimate promises for the future."

He died in 1878. The following account of the discovery of glycogen is taken from his *Nouvelle Fonction du Foie* (Paris, 1853):—

"My first researches into the assimilation and destruction of sugar in the living organism were made in 1843: and in my inaugural thesis (Dec. 1843) I published my first experiments on the subject. I succeeded in demonstrating a fact hitherto unknown, that cane-sugar cannot be directly destroyed in the blood. If you inject even a very small quantity of cane-sugar, dissolved in water, into the blood or under the skin

of a rabbit, you find it again in the urine unchanged, with all its chemical properties the same. . . . I had soon to give up my first point of view, because this question of the existence of a sugar-producing organ, that I had thought such a hard problem of physiology, was really the first thing revealed to me, as it were of itself, at once."

He kept two dogs on different diets, one with sugar, the other without it; then killed them during digestion, and tested the blood in the hepatic veins :—

"What was my surprise, when I found a considerable quantity of sugar in the hepatic veins of the dog that had been fed on meat only, and had been kept for eight days without sugar: just as I found it in the other dog that had been fed for the same time on food rich in sugar. . . .

"Finally, after many attempts—*après beaucoup d'essais et plusieurs illusions que je fus obligé de rectifier par des tâtonnements*—I succeeded in showing, that in dogs fed on meat the blood passing through the portal vein does not contain sugar before it reaches the liver; but when it leaves the liver, and comes by the hepatic veins into the inferior vena cava, this same blood contains a considerable quantity of a sugary substance (glucose)."

His further discovery, that this formation of sugar is increased by puncture of the floor of the fourth ventricle, was published in 1849. It is impossible to exaggerate the importance of Claude Bernard's single-handed work in this field of physiology and pathology :—

"As a mere contribution to the history of sugar

within the animal body, as a link in the chain of special problems connected with digestion and nutrition, its value was very great. Even greater, perhaps, was its effect as a contribution to general views. The view that the animal body, in contrast to the plant, could not construct, could only destroy, was, as we have seen, already being shaken. But evidence, however strong, offered in the form of numerical comparisons between income and output, failed to produce anything like the conviction which was brought home to every one by the demonstration that a substance was actually formed within the animal body, and by the exhibition of the substance so formed.

"No less revolutionary was the demonstration that the liver had other things to do in the animal economy besides secreting bile. This, at one blow, destroyed the then dominant conception that the animal body was to be regarded as a bundle of organs, each with its appropriate function, a conception which did much to narrow inquiry, since when a suitable function had once been assigned to an organ there seemed no need for further investigations. . . .

"No less pregnant of future discoveries was the idea suggested by this newly-found-out action of the hepatic tissue, the idea happily formulated by Bernard as 'internal secretion.' No part of physiology is at the present day being more fruitfully studied than that which deals with the changes which the blood undergoes as it sweeps through the several tissues, changes by the careful adaptation of which what we call the health of the body is secured, changes the failure or discordance of which entails disease. The study of these internal secretions constitutes a path of inquiry which has

already been trod with conspicuous success, and which promises to lead to untold discoveries of the greatest moment; the gate to this path was opened by Bernard's work." (Sir M. Foster, *loc. cit.*)

But the work to be done, before all the clinical facts of the disease can be stated in terms of physiology, is not yet finished. In England, especial honour is due to Dr Pavy for his life-long study of this most complex problem.

V

THE PANCREAS

HERE again Claude Bernard's name must be put first. Before him, the diverse actions of the pancreatic juice had hardly been studied. Vesalius, greatest of all anatomists, makes no mention of the duct of the pancreas, and speaks of the gland itself as though its purpose were just to support the parts in its neighbourhood — *ut ventriculo instar substerniculi ac pulvinaris subjiciatur.* The duct was discovered by Wirsung, in 1642: but anatomy could not see the things that belong to physiology. Lindanus (1653) said, *I cannot doubt that the pancreas expurgates, in the ordinary course of Nature, those impurities of the blood that are too crass and inept to be tamed by the spleen: and, in the extraordinary course, all black bile, begotten of disease or intemperate living.* Wharton (1656) said, *It ministers to the nerves, taking up certain of their superfluities, and remitting them through its duct into the intestines.* And Tommaso Bartholini (1666) called it the *biliary vesicle of the spleen.*

This chaos of ideas was brought into some sort

of order by Regnier de Graaf, pupil of François de Bois (Sylvius). De Bois had guessed that the pancreas must be considered not according to its position in the body, but according to its structure: that it was analogous to the salivary glands. He urged his pupil to make experiments on it: and de Graaf says:—

"I put my hand to the work: and though many times I despaired of success, yet at last, by the blessing of God on my work and prayers, in the year 1660 I discovered a way of collecting the pancreatic juice."

And, by further experiment, he refuted Bartholini's theory that the pancreas was dependent on the spleen.

Sylvius had supposed that the pancreatic juice was slightly acid, and de Graaf failed to note this mistake; but it was corrected by Bohn's experiments in 1710.

Nearly two hundred years come between Regnier de Graaf and Claude Bernard: it is no wonder that Sir Michael Foster says that de Graaf's work was "very imperfect and fruitless." So late as 1840, there was yet no clear understanding of the action of the pancreas. Physiology could not advance without organic chemistry; de Graaf could no more discover the amylolytic action of the pancreatic juice than Galvini could invent wireless telegraphy. The physiologists had to wait till chemistry was ready to help them:—

"Of course, while physical and chemical laws

were still lost in a chaos of undetermined facts, it was impossible that men should analyse the phenomena of life: first, because these phenomena go back to the laws of chemistry and physics; and next, because they cannot be studied without the apparatus, instruments, and all other methods of analysis that we owe to the laboratories of the chemists and the physicists." (Cl. Bernard, *Phys. Opér.*, p. 61.)

Therefore de Graaf failed, because he got no help from other sciences. But it cannot be called failure; he must be contrasted with the men of his time, Lindanus and Bartholini, facts against theories, not with men of this century. And Claude Bernard went back to de Graaf's method of the fistula, having to guide him the facts of chemistry observed by Valentin, Tiedemann and Gmelin, and Eberlé. His work began in 1846, and the Académie des Sciences awarded a prize to it in 1850:—

"Let this vague conception (the account of the pancreas given in Johannes Müller's Text-book of Physiology) be compared with the knowledge which we at present have of the several distinct actions of the pancreatic juice, and of the predominant importance of this fluid not only in intestinal digestion but in digestion as a whole, and it will be at once seen what a great advance has taken place in this matter since the early forties. That advance we owe in the main to Bernard. Valentin, it is true, had in 1844 not only inferred that the pancreatic juice had an action on starch, but confirmed his view by actual experiment with the juice expressed from the gland; and

Eberlé had suggested that the juice had some action on fat; but Bernard at one stroke made clear its threefold action. He showed that it on the one hand emulsified, and on the other hand split up, into fatty acids and glycerine, the neutral fats; he clearly proved that it had a powerful action on starch, converting it into sugar; and lastly, he laid bare its remarkable action on proteid matters." (Sir Michael Foster, *loc. cit.*)

Finally came the discovery that the pancreas —apart from its influences on digestion—contributes its share, like the ductless glands, to the general chemistry of the body:—

"It was discovered, a few years ago, by von Mering and Minkowski, that if, instead of merely diverting its secretion, the pancreas is bodily removed, the metabolic processes of the organism, and especially the metabolism of carbo-hydrates, are entirely deranged, the result being the production of permanent diabetes. But if even a very small part of the gland is left within the body, the carbo-hydrate metabolism remains unaltered, and there is no diabetes. The small portion of the organ which has been allowed to remain (and which need not even be left in its proper place, but may be transplanted under the skin or elsewhere) is sufficient, by the exchanges which go on between it and the blood generally, to prevent those serious consequences to the composition of the blood, and the general constitution of the body, which result from the complete removal of this organ." (Prof. Schäfer, 1894.)

Here, in this present study of "pancreatic

diabetes," by Dr Vaughan Harley and others, are facts as important as any that Bernard made out: in no way contradicting his work, but added to it. The pancreas is no longer taken to be only a sort of salivary gland out of place: over and above the secretion that it pours into the intestines, it has an "internal secretion," a constituent of the blood: it belongs not only to the digestive system, but also, like the thyroid gland and the supra-renal capsules, to the whole chemistry of the blood and the tissues. So far has physiology come, unaided by anatomy, from the fantastic notions of Lindanus and the men of his time: and has come every inch of the way by the help of experiments on animals. And it is worthy of note, that Professor Starling's recent observations, on the chemical influence of the duodenal mucous membrane on the flow of pancreatic fluid, have advanced the subject still further, and have given a new fact of very great interest to physiology.

VI

THE GROWTH OF BONE

THE work of du Hamel proved that the periosteum is one chief agent in the growth of bone. Before him, this great fact of physiology was unknown; for the experiments made by Anthony de Heide (1684), who studied the production of callus in the bones of frogs, were wholly useless, and serve only to show that men in his time had no clear understanding of the natural growth of bone. De Heide says of his experiments :—

"From these experiments it appears—*forsan probatur*—that callus is generated by extravasated blood, whose fluid particles being slowly exhaled, the residue takes the form of the bone: which process may be further advanced by deciduous halitus from the ends of the broken bone."

And Clopton Havers, in his *Osteologia Nova* (London, 1691), goes so far the wrong way that he attributes to the periosteum not the production of bone, but the prevention of over-production; the periosteum is put round the shaft of a bone to compress it, lest it grow too large.

Du Hamel's discovery (1739-1743) came out of a chance observation, made by John Belchier,* that the bones of animals fed near dye-works were stained with the dye. Belchier therefore put a bird on food mixed with madder, and found that its bones had taken up the stain. Then du Hamel studied the whole subject by a series of experiments. To estimate the advance that he gave to physiology, contrast de Heide's fanciful language with the title of one of du Hamel's papers—*Quatrième Mémoire sur les Os, dans lequel on se propose de rapporter de nouvelles preuves qui établissent que les os croissent en grosseur par l'addition de couches osseuses qui tirent leur origine du périoste, comme le corps ligneux des Arbres augmente en grosseur par l'addition de couches ligneuses qui se forment dans l'écorce.* Or take an example of du Hamel's method :—

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* "An Account of the Bones of Animals being changed to a red Colour by Aliment only," by John Belchier, F.R.S., *Phil. Trans. Roy. Soc.*, 1735-36. There is a letter from Sir Hans Sloane, then President of the Royal Society, to M. Geoffroy, member of the French Academy :—"M. Belchier, chirurgien, membre de cette Société, dînant un jour chez un Teinturier qui travaille en Toiles peintes, remarqua que dans un Porc frais qu'on avoit servi sur table, et dont la chair étoit de bon goût, les os étoient rouges. Il demanda la cause d'un effet si singulier, et on lui dit que ces sortes de Teinturiers se servoient de la racine de Rubia Tinctorum, ou garence, pour fixer les couleurs déjà imprimées sur les Toiles de cotton, qu'on appelle en Angleterre callicoes." This passage of dye into the bones of animals had been noted so far back as 1573, by Antoine Mizald, a doctor in Paris—*Erythrodanum, vulgo rubia tinctorum, ossa pecudum rubenti et sandycino colore imbuit*

"Three pigs were destined to clear up my doubts. The first, six weeks old, was fed for a month on ordinary food, with an ounce daily of madder-juice—*garence grappe*—put in it. At the end of the month, we stopped the juice, and fed the pig in the ordinary way for six weeks, and then killed it. The marrow of the bones was surrounded by a fairly thick layer of white bone: this was the formation of bone during the first six weeks of life, without madder. This ring of white bone was surrounded by another zone of red bone: this was the formation of bone during the administration of the madder. Finally, this red zone was covered with a fairly thick layer of white bone: this was the layer formed after the madder had been left off. . . . We shall have no further difficulty in understanding whence transudes the osseous juice that was thought necessary for the formation of callus and the filling-up of the wounds of the bones, now we see that it is the periosteum that fills up the wounds, or is made thick round the fractures, and afterward becomes of the consistence of cartilage, and at last acquires the hardness of bones."

These results, confirmed by Bazan (1746) and Boehmer (1751), were far beyond anything that had yet been known about the periosteum. But the growth of bone is a very complex process: the naked eye sees only the grosser changes that come with it; and du Hamel's ingenious comparison between the periosteum and the bark of trees was too simple to be exact. Therefore his work was opposed by Haller, and by Dethleef, Haller's pupil: and the great authority of Haller's name, and the difficulties lying beyond du Hamel's plain facts,

brought about a long period of uncertainty. Bordenave (1756) found reasons for supporting Haller; and Fougeroux (1760) supported du Hamel. Thus men came to study the whole subject with more accuracy—the growth in length, as well as the growth in thickness; the medullary cavity, the development of bone, the nutrition and absorption of bone. Among those who took up the work were Bichat, Hunter, Troja, and Cruveilhier; and they recognised the surgical aspect of these researches in physiology. After them, the periosteal growth of bone became, as it were, a part of the principles of surgery. From this point of view of practice, issued the experiments made by Syme (1837) and Stanley (1849): which proved the importance of the epiphysial cartilages for the growth of the bones in length, and the risk of interfering with these cartilages in operations on the joints of children. Finally, with the rise of anæsthetics and of the antiseptic method, came the work of Ollier, of Lyon, whose good influence on the treatment of these cases can hardly be overestimated.

VII

THE NERVOUS SYSTEM

AS with the circulatory system, so with the nervous system, the work of Galen was centuries ahead of its time. Before him, Aristotle, who twice refers to experiments on animals, had observed the brain during life: for he says, "In no animal has the blood any feeling when it is touched, any more than the excretions; nor has the brain, or the marrow, any feeling when it is touched": but there is reason for believing that he neither recognised the purpose of the brain, nor understood the distribution of the nerves. Galen, by the help of the experimental method, founded the physiology of the nervous system:—

"Galen's method of procedure was totally different to that of an anatomist alone. He first reviewed the anatomical position, and by dissection showed the continuity of the nervous system, both central and peripheral, and also that some bundles of nerve fibres were distributed to the skin, others to the muscles. Later, by process of the physiological experiment of dividing such bundles of fibres, he showed that the former were sensory fibres

and the latter motor fibres. He further traced the nerves to their origins in the spinal cord, and their terminations as aforesaid. From these observations and experiments he was able to deduce the all-important fact that different nerve-roots supplied different groups of muscles and different areas of the skin. . . . An excellent illustration of his method, and of the fact that we ought not to treat symptoms, but the causes of symptoms, is shown very clearly in one of the cases which Galen records as having come under his care. He tells us that he was consulted by a certain sophist called Pausanias, who had a severe degree of anæsthesia of the little and ring fingers. For this loss of sensation, etc., the medical men who attended him applied ointments of various kinds to the affected fingers; but Galen, considering that that was a wrong principle, inquired into the history, and found that while the patient was driving in his chariot he had accidentally fallen out and struck his spine at the junction of the cervical and dorsal regions. Galen recognised that he had to do with a traumatism affecting the eighth cervical and first dorsal nerve; therefore, he says, he ordered that the ointments should be taken off the hand and placed over the spinal column, so as to treat the really affected part, and not apply remedies to merely the referred seat of pain."*

Galen, by this sort of work, laid the foundations of physiology; but the men who came after him let his facts be overwhelmed by fantastic doctrines:

* From an address on Galen, given by Sir Victor Horsley before the Medical Society of the Middlesex Hospital. See *Middlesex Hospital Journal*, May 1899.

all through the ages, from Galen to the Renaissance, no great advance was made toward the interpretation of the nervous system. Long after the Renaissance, his authority still held good; his ghost was not laid even by Paracelsus and Vesalius, it haunted the medical profession so late as the middle of the seventeenth century; but the men who worshipped his name missed the whole meaning of his work. This long neglect of the experimental method left such a gap in the history of physiology, that Sir Charles Bell seems to take up the experimental study of the nervous system at the point where Galen had stopped short; we go from the time of Commodus to the time of George the Third, and there is Bell, as it were, putting the finishing touch to Galen's facts. It is true that experiments had been made on the nervous system by many men; but a dead weight of theories kept down the whole subject. For a good instance, how imagination hindered science, there is the following list, made by Dr Risien Russell, of theories about the cerebellum :—

"Galen was of opinion that the cerebellum must be the originator of a large amount of vital force. After him, and up to the time of Willis, the prevalent idea seems to have been that it was the seat of memory; while Bourillon considered it the seat of instinct and intelligence. Willis supposed that it presided over involuntary movements and organic functions; and this view, though refuted by Haller, continued in the ascendency for some time. Some believed strongly in its influence on the functions of organic life; and according to some,

diseases of the cerebellum appeared to tell on the movements of the heart. . . . Haller believed it to be the seat of sensations, as well as the source of voluntary power; and there were many supporters of the theory that the cerebellum was the seat of the sensory centres. Renzi considered this organ the nervous centre by which we perceive the reality of the external world, and direct and fix our senses on the things round us. Gall, and later Broussais, and others, held that this organ presided over the instinct of reproduction, or the propensity to love; while Carus regarded it as the seat of the will also. Rolando looked on it as the source of origin of all movements. Jessen adduced arguments in favour of its being the central organ of feeling, or of the soul, and the principal seat of the sensations."

It is plain, from this list, that physiology had become obscured by fanciful notions of no practical value. If a better understanding of the nervous system could have been got without experiments on animals, why had men to wait so long for it? The Italian anatomists had long ago given them all the anatomy that was needed to make a beginning; the hospitals, and practice, had given them many hundred years of clinical facts; nervous diseases and head injuries were common enough in the Middle Ages; and by the time of Ambroise Paré, if not before, *post-mortem* examinations were allowed. The one thing wanted was the experimental method; and, for want of it, the science of the nervous system stood still. Experiments had been made; but the steady, general, unbiassed use

of this method had been lost sight of, and men were more occupied with logic and with philosophy.

Then, in 1811, came Sir Charles Bell's work. If any one would see how great was the need of experiments on animals for the interpretation of the nervous system, let him contrast the physiology of the eighteenth century with that one experiment by Bell which enabled him to say, "I now saw the meaning of the double connection of the nerves with the spinal marrow." It is true that this method is but a part of the science of medicine; that experiment and experience ought to go together like the convexity and the concavity of a curve. But it is true also that men owe their deliverance from ignorance about the nervous system more to experiments on animals than to any other method of observing facts.

1. *Sir Charles Bell* (1778-1842).

The great authority of Sir Charles Bell has been quoted a thousand times against all experiments on animals:—

"Experiments have never been the means of discovery; and a survey of what has been attempted of late years in physiology, will prove that the opening of living animals has done more to perpetuate error than to confirm the just views taken from the study of anatomy and natural motions."

He wrote, of course, in the days before bacteriology, before anæsthetics; he had in his mind neither inoculations, nor any observations made under

chloroform or ether, but just "the opening of living animals." He had also in his mind, and always in it, a great dislike against the school of Magendie. Let all that pass; our only concern here is to know whether these words are true of his own work.

They occur in a paper, *On the Motions of the Eye, in Illustration of the Uses of the Muscles and Nerves of the Orbit;* communicated by Sir Humphry Davy to the Royal Society, and read March 20, 1823.* This essay was one of a series of papers on the nervous system, presented to the Royal Society during the years 1821-1829. In 1830, having already published four of these papers under the title, "The Exposition of the Nervous System," Bell published all six of them, under the title, "The Nervous System of the Human Body."

In his Preface to this book (1830) he quotes the earliest of all his printed writings on the nervous system, a pamphlet, printed in 1811, under the title, *An Idea of a New Anatomy of the Brain, Submitted for the Observation of the Author's Friends.* We have therefore two statements of his work, one in 1811, the other in 1823 and 1830. The first of them was written when his work was still new before his eyes.

Those who say that experiments did not help Bell in his great discovery—the difference between

* This paper includes an *Experimental Enquiry into the Action of these Muscles*, giving an account of an experiment on the eye.

the anterior and the posterior nerve-roots—appeal to certain passages in the 1830 volume:—

"In a foreign review of my former papers, the results have been considered as a further proof in favour of experiments. They are, on the contrary, deductions from anatomy; and I have had recourse to experiments, not to form my own opinions, but to impress them upon others. It must be my apology that my utmost efforts of persuasion were lost, while I urged my statements on the grounds of anatomy alone. I have made few experiments; they have been simple and easily performed, and I hope are decisive. . . .

"My conceptions of this matter arose by inference from the anatomical structure; so that the few experiments which have been made were directed only to the verification of the fundamental principles on which the system is established."

If it were not for the 1811 pamphlet, the opponents of all experiments on animals might claim Sir Charles Bell on their side. But while his work was still a new thing, he spoke in another way of it:—

"I found that injury done to the anterior portion of the spinal marrow convulsed the animal more certainly than injury to the posterior portion; but I found it difficult to make the experiment without injuring both portions.

"Next, considering that the spinal nerves have a double root, and being of opinion that the properties of the nerves are derived from their connections with the parts of the brain, *I thought that I had an opportunity of putting my opinion to*

the test of experiment, and of proving at the same time that nerves of different endowments were in the same cord (nerve-trunk) and held together by the same sheath.

"On laying bare the roots of the spinal nerves, I found that I could cut across the posterior fasciculus of nerves, which took its origin from the posterior portion of the spinal marrow, without convulsing the muscles of the back; but that on touching the anterior fasciculus with the point of the knife, the muscles of the back were immediately convulsed.

"*Such were my reasons for concluding* that the cerebrum and cerebellum were parts distinct in function, and that every nerve possessing a double function obtained that by having a double root. *I now saw the meaning* of the double connection of the nerves with the spinal marrow; and also the cause of that seeming intricacy in the connections of nerves throughout their course, which were not double at their origins."

It is impossible to reconcile the 1830 sentences with this vivid personal account of himself; *I had an opportunity of putting my opinion to the test of experiment . . . an opportunity of proving. . . . Such were my reasons for concluding. . . . I now saw. . . .* It is just what all men of science say of their experiments: the very phrase of Archimedes, and Asellius, and de Graaf. If Sir Charles Bell had been working at the facts of chemistry or of botany, who would have doubted the meaning of these words?

This same inconsistency of sentences occurs elsewhere in his *Nervous System of the Human*

Body. In one place he says that he has made few experiments: *They have been simple, and easily performed, and I hope are decisive.* In another he says: "*After making several experiments on the cerebrum and cerebellum, I laid the question of their functions entirely aside,* and confined myself to the investigation of the spinal marrow and the nerves; *a subject which I found more within my power,* and which forms the substance of the present volume."

Next, take his account of the cranial nerves:—

"It was necessary to know, in the first place, whether the phenomena exhibited on injuring the separate roots corresponded with what was suggested by their anatomy. . . .

"Here a difficulty arose. An opinion prevailed that ganglions were intended to cut off sensation; and every one of these nerves, which I supposed were the instruments of sensation, have ganglions on their roots. Some very decided experiment was necessary to overturn this dogma. (Account of the experiment.) By pursuing the inquiry, it was found that a ganglionic nerve is the sole organ of sensation in the head and face: ganglions were therefore no hindrance to sensation; and thus my opinion was confirmed. . . . *It now became obvious* why the third, sixth, and ninth nerves of the encephalon were single nerves in their roots. . . .

"Observing that there was a portion of the fifth nerve which did not enter the ganglion of that nerve, and being assured of the fact by the concurring testimony of anatomists, I conceived that the fifth nerve was in fact the uppermost nerve of the spine. . . . This opinion was confirmed by experiment. . . . (Account of an experiment on the

dead body.) On dividing the root of the nerve in a living animal, the jaw fell relaxed. Thus its functions are no longer matter of doubt: it is at once a muscular nerve and a nerve of sensibility. And thus the opinion is confirmed, that the fifth nerve is to the head what the spinal nerves are to the other parts of the body, in respect to sensation and volition."

The value of the experimental method could hardly be stated in more emphatic words. He supposed something, conceived it, had an opinion about it. Anatomy had suggested something to him. He put his opinion to the test of phenomena, that is to say, to the test of visible facts; and then his opinion was confirmed. As with the spinal nerve-roots, so with the fifth cranial nerve—his work was successful, because he followed the way of experiment.

He was by nature of a most complex and sensitive temperament, full of contrary forces—one man in 1811, another in 1830. In 1811 he wrote, *I now saw the meaning of the double connection of the nerves;* in 1830 he had come to hate the *stupid sterile materialism* of the French school: he beheld anatomy falling behind physiology, and his Windmill Street school perishing to make way for the Hospital schools and for the University of London. He was before everything else a great anatomist: he stood up for the honour of anatomy against the new physiology, and for the honour of the Monroes and the Hunters against Magendie: he hated the notion that any man should proceed to experiments

on function till the very last secrets had been got out of structure. He died a few years afterward. The 1830 writings are his last stand for the defence of his country, his school, and his beloved anatomy, against the methods of Magendie; who said of himself, "I am a mere street scavenger, *chiffonier*, of science. With my hook in my hand and my basket on my back, I go about the streets of science, collecting what I find."

This open conflict between Bell's first and last thoughts is a part of his character: he was brilliant, impulsive, changeable, inconsistent; and, what is more important, his honour kept him from trying to evade this trumpery charge of inconsistency; and he reprinted the 1811 Preface in the book that he published in 1830. Doubtless he would have picked his words more carefully if he had foreseen that one of the 1830 sentences would be wrested out of its place in his life's work, and used as false evidence against the very method that he followed.

His observations on the cranial nerves brought about an immediate change in the practice of surgery:—

"Up to the time that Sir Charles Bell made his experiments on the nerves of the face, it was the common custom of surgeons to divide the facial nerve for the relief of neuralgia, *tic douloureux;* whereas it exercises, and was proved by Sir Charles Bell to exercise, no influence over sensation, and its division consequently for the relief of pain was a useless operation." (Sir J. Erichsen.)

The relation of Magendie's work on the nerve-roots to Bell's work need not be considered here. The exact dates of Bell's observations are given by one of his pupils in the Preface to the 1830 volume. Magendie finally proved the sensory nature of the posterior nerve-roots: "The exact and full proof which he brought forward of the truth which Charles Bell had divined rather than demonstrated, that the anterior and posterior roots of spinal nerves have essentially different functions—a truth which is the very foundation of the physiology of the nervous system—is enough by itself to mark him as a great physiologist." (Sir M. Foster, *loc. cit.*)

2. *Marshall Hall* (1790-1857).

Reflex action had been studied long before the time of Marshall Hall. The Hon. Robert Boyle (1663) had observed the movements and actions of decapitated vipers, flies, silkworms, and butterflies. Similar observations were made on frogs, eels, and other lower animals, by Redi, Woodward, Stuart, Le Gallois, and Sir Gilbert Blane. According to Richet, it was Willis who first gave the name *reflex* to these movements.

It cannot be said that these first studies of reflex action did much for physiology. But the following translation from Prochaska (1800) shows how they cleared the way for Marshall Hall's work, by the proof that they gave of the liberation of nervous energy in the spinal cord :—

"These movements of animals after decapitation must needs be by consent and commerce

betwixt the spinal nerves. For a decapitated frog, if it be pricked, not only draws away the part that is pricked, but also creeps and jumps; which cannot happen but by consent betwixt the sensory nerves and the motor nerves. The seat of which consent must needs be in the spinal cord, the only remaining portion of the sensorium. *And this reflexion of sensory impressions into motor impressions is not accomplished in obedience to physical laws alone—wherein the angle of reflexion is equal to the angle of incidence, and reaction to action—but it follows special laws as it were written by Nature on the spinal cord, which we can know only by their effects, but cannot fathom with the understanding.* But the general law, whereby the sensorium reflects sensory impressions into motor impressions, is the preservation of ourselves."

It was not possible, in 1800, to go further, or to put the facts of reflex action more clearly: but this fine sentence gives no hint of the truth that guided Marshall Hall—that the "consent and commerce" of reflex action are to be found at definite points or levels in the spinal cord; that the cord no more "works as a whole" than the brain. The greatness of Marshall Hall's work lies in his recognition of the divisional action of the cord: he proved the existence of definite centres in it, he discovered the facts of spinal localisation, and thus foreshadowed the discovery of cerebral localisation. In his earlier writings (1832-33) he showed how the movements of the trunk and of the limbs are only one sort of reflex action; how the larynx, the pharynx, and the sphincter muscles, all act by the "consent and

commerce" of the spinal cord. Later, in 1837, he demonstrated the course of nerve-impulses along the cord from one level to another, the results of direct stimulation of the cord, and other facts of spinal localisation. He noted the different effects of opium and of strychnine on reflex action; and he extended the doctrines of reflex action beyond physiology to the convulsive movements of the body in certain diseases.

3. *Flourens* (1794-1867).

Beside his work on the nervous system, Flourens studied the periosteal growth of bone, and the action of chloroform; * but he is best known by his experiments on the respiratory centre and the cerebellum. The men who interpreted the nervous system followed the anatomical course of that system: first the nerve-roots, then the cord, then the medulla oblongata and the cerebellum, and last the cerebral hemispheres; a steady upward advance, from the observation of decapitated insects to the localisation of centres in the human brain. Flourens, by his work on the medulla oblongata, localised the respiratory centre, the nerve-cells for the reflex movements of respiration :—

* When Flourens died, Claude Bernard was appointed to his place in the French Academy; and, in the *Discours de Reception* (May 27, 1869), said, "It is twenty-two years since the discovery of anæsthesia by ether came to us from the New World, and spread rapidly over Europe. M. Flourens was the first man who showed that chloroform is more active than ether."

"M. Flourens a circonscrit ce centre avec une scrupuleuse précision, et lui a donné le nom de *nœud vital.*" (Cl. Bernard.)

Afterward came the discovery of cardiac and other centres in the same portion of the nervous system. Flourens also showed that the cerebellum is concerned with the equilibration of the body, and with the co-ordination of muscular movements; that an animal, a few days old, deprived of sensation and consciousness by removal of the cerebral hemispheres, was yet able to stand and move forward, but, when the cerebellum was removed, its muscles lost all co-ordinate action. (*Recherches Expérimentales*, Paris, 1842.) And from his work, and the work of those who followed him, on the semicircular canals of the internal ear, came the evidence that these minute structures are the terminal organs of equilibration: that as the special senses have their terminal apparatus and their central apparatus, so the semicircular canals and the cerebellum are the terminal apparatus and the central apparatus of the sense of equilibrium.

4. *Claude Bernard* (1813-1878).

The discovery of the vaso-motor nerves, and of the control of the nervous system over the calibre of the arteries, was made by Claude Bernard at the outset of his work on the influence of the nervous system on the temperature.* The evidence of

* A full account of this discovery, and of its relation to the experiments of Brown Séquard, Waller, and Budge, is given

Professor Sharpey before the Royal Commission of 1875 shows how things had been misjudged, before Bernard's time, in the light of "views taken from the Study of Anatomy and Natural Motions":—

"I remember that Sir Charles Bell gave the increased size of the vessels in blushing, and their fulness of blood, as an example of the increased action of the arteries in driving on the blood. It turns out to be just the reverse, inasmuch as it is owing to a paralysis of the nerves governing the muscular coats of the arteries."

Claude Bernard's first account of his work was communicated to the Société de Biologie in December 1851. The following description is taken from his *Leçons de Physiologie Opératoire*:—

"I will remind you how I was led to the discovery of the vaso-motor nerves. Starting from the clinical observation, made long ago, that in paralysed limbs you find at one time an increase of cold, and at another an increase of heat, I thought this contradiction might be explained by supposing that, side by side with the general action of the nervous system, the sympathetic nerve might have the function of presiding over the production of heat; that is to say, that in the case where the

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by Sir Michael Foster in his life of Claude Bernard; and the question of priority between Bernard and Brown Séquard need not be considered here, for the experimental method was the only way open to either of them. For an account of the work done, before Bernard, in this field of physiology, see Prof. Stirling's admirable and learned monograph, *Some Apostles of Physiology* (Waterlow & Sons, London, 1902), page 104.

paralysed limb was chilled, I supposed the sympathetic nerve to be paralysed, as well as the motor nerves; while in the paralysed limbs that were not chilled, the sympathetic nerve had retained its function, the systemic nerves alone having been attacked.

"This was a theory, that is to say, an idea leading me to make experiments; and for these experiments I must find a sympathetic nerve-trunk of sufficient size, going to some organ that was easy to observe, and must divide this trunk to see what would happen to the heat-supply of the organ. You know that the rabbit's ear, and the cervical sympathetic nerve of this animal, offered us the required conditions. So I divided the nerve; and immediately my experiment gave the lie direct to my theory—*Je coupai donc ce filet et aussitôt l'expérience donna à mon hypothèse le plus éclatant démenti.* I had thought that the section of the nerve would suppress the function of nutrition, of calorification, over which the sympathetic system had been supposed to preside, and would cause the hollow of the ear to become chilled; and here was just the opposite, a very warm ear, with great dilatation of its vessels.

"I need not remind you how I made haste to abandon my first theory, and gave myself to the study of this new state of things. And you know that here was the starting-point of all my researches into the vaso-motor and thermic system; and the study of this subject is become one of the richest fields of experimental physiology."

Waller, in 1853, studied the vaso-motor centre in the spinal cord; and Schiff, in 1856, found evidence of the existence of two kinds of vaso-motor

nerves—those that constrict the vessels, and those that dilate them. This view was finally established in 1858 by Claude Bernard's experiments on the chorda tympani and the submaxillary gland.

The *Leçons de Physiologie Opératoire* were published in 1879. Twenty years later, Sir Michael Foster says of Bernard's work:—

"It is almost impossible to exaggerate the importance of these labours of Bernard on the vaso-motor nerves, since it is almost impossible to exaggerate the influence which our knowledge of the vaso-motor system, springing as it does from Bernard's researches as from its fount and origin, has exerted, is exerting, and in widening measure will continue to exert, on all our physiological and pathological conceptions, on medical practice, and on the conduct of human life. There is hardly a physiological discussion of any width in which we do not sooner or later come on vaso-motor questions. Whatever part of physiology we touch, be it the work done by a muscle, be it the various kinds of secretive labour, be it the insurance of the brain's well-being in the midst of the hydrostatic vicissitudes to which the changes of daily life subject it, be it that maintenance of bodily temperature which is a condition of the body's activity; in all these, as in many other things, we find vaso-motor factors intervening. And if, passing the insecure and wavering line which parts health from illness, we find ourselves dealing with inflammation, or with fever, or with any of the disordered physiological processes which constitute disease, we shall find, whatever be the tissue specially affected by the morbid conditions, that vaso-

motor influences have to be taken into account. The idea of vaso-motor action is woven as a dominant thread into all the physiological and pathological doctrines of to-day; attempt to draw out that thread, and all that would be left would appear as a tangled heap."

5. *Cerebral Localisation.*

Finally, moving upward along the anatomy of the nervous system, physiology came to study the motor-centres and special sense-centres of the cerebral hemispheres. The year 1861 may fairly be said to mark the beginning of the discovery of these centres, when Broca, at a meeting of the Anthropological Society of Paris, heard Aubertin's paper on the connection between the frontal convolutions and the faculty of speech. But, of course, some sort of belief in cerebral localisation had been in the air long before Broca's time. Willis (1621-1675), who was contemporary with Sir Isaac Newton, had written of the brain as though its convolutions, or "cranklings" as he called them, showed that its work was departmental:—

"As the animal spirits for the various acts of imagination and memory ought to be moved within certain and distinct limits, or bounded places, and these motions to be often iterated or repeated through the same tracts or paths, for that reason these manifold convolutions and infoldings of the brain are required for these divers manners of ordinations of the animal spirits—to wit, that in these cells or storehouses, severally placed, might

be kept the species of sensitive things, and as occasion serves, may be taken from thence."*

And Gall, a century after Willis, had collected and published, in support of his system of phrenology, many cases and *post-mortem* examinations showing the differentiation of the work of the brain. Gall is a warning for all time against the dangers of deduction; he had but one idea, and he drove it to death; but the clinical and pathological facts which he amassed, in the hope of establishing a set of doctrines out of all relation to facts, are as true now as ever; and, if he had been content to go the way of induction, and to set himself to the accumulation of facts, he might have become a great physiologist. In his knowledge of the anatomy of the brain, and in the dissection of the brain, he was far ahead of the men of his time; but he followed his own imaginings, and left nothing that could last, except those cases and pathological instances that are buried in the ruins of his system. But there they are, and are still of value. For example, Gall's case of loss of speech, after an injury involving the speech-centres, ought to have commanded the attention of all physiologists: but it came to nothing, because he used it to support his doctrine of organs and bumps, and it shared the fate of that doctrine. Phrenology is gone past recall; it died of that con-

* For an account of Willis' work on the nervous system, see Sir Victor Horsley's *Fullerian Lectures*, 1891. Willis was the first, or one of the first, to recognise the fact that the cerebral ventricles are nothing more than lymph-cavities.

genital disease, the deductive fallacy; but there was a time when it might have been turned to the service of science.

The excitement that Gall aroused by the spread of his ideas shows that some belief in cerebral centres was waiting for development. All men are by nature phrenologists; the commonplace excuses that are offered for lapses of memory, venial offences, and inherited weaknesses, all appeal to the comfortable notion that the offender is not wholly perverted, and that some very small and strictly localised group of cells is at fault. And it is probable that the physiology of the central nervous system, with its present strong tendency toward psychology, will some day be back, at a far higher level, above the point where phrenology went wrong. As Mme. de Staël said, *L'esprit humain fait progrès toujours, mais c'est progrès en spirale.* But the question, whether the general desire for a rational system of psychology will ever commend itself to physiology, belongs to the future. All that is of present concern is the steady, continuous, and successful advance, by the way of induction, and by the help of experiments on animals, toward a clear and accurate statement of the departmental work of the brain.

It is one of many instances how science and practice work together, that the modern study of these centres began not in experiment but in experience. The first centres that were thus studied were the speech-centres; and the observation of them arose out of the cases recorded by Bouillard in

1825, and Dax in 1836. Clinical observation, and *post-mortem* examination, found the speech-centres; physiological experiments had nothing to do with it; and phrenology had, as it were, found them, and then lost them. But at once, so soon as practice gave the word to science, physiology set to work. These clinical facts had been there all the time; loss of speech had gone with disease or injury of "Broca's convolution" ever since man had been on the earth, and nobody had seen the significance of this sequence. Then, after 1861, everything was changed; and in a few years physiology had mapped out a large part of the surface of the brain, and had charted the motor-centres.

The story of Broca's convolution is told in Hamilton's *Text-Book of Pathology*:—

"In 1825, Bouillard collected a series of cases to show that the faculty of speech resided in the frontal lobes. In the year 1836 M. Dax, in a paper read to the Medical Congress of Montpellier, stated as a result of his researches that, where speech was lost from cerebral causes, he believed the lesion was invariably found in the left cerebral hemisphere, and that the accompanying paralysis of the right side of the body is consequent upon this. This paper for long lay buried in the annals of medical literature, but was unearthed years afterwards by his son, and presented to the French Academy. Bouillard's views were also disinterred by Aubertin, and in the year 1861 were brought by him before the notice of the Anthropological Society of Paris. Broca, who was present at the meeting, had a

patient under his care at the time who had been aphasic (without power of speech) for twenty-one years, and who was in an almost moribund state. The autopsy proved of great interest, as it was found that the lesion was confined to the left side of the brain, and to what we now call the third frontal convolution. Broca was struck with the coincidence; and when a similar case came under his care afterwards, unaware of what had been done by Dax, he postulated the conclusion that the integrity of the third frontal convolution, and perhaps also part of the second, is essential to speech. In a subsequent series of fifteen typical cases examined, it was found that the lesion had destroyed, among other parts, the posterior part of the third frontal in fourteen. In the fifteenth case the destruction had taken place in the island of Reil and temporal lobe."

After 1861, physiology took the lead, and kept it. But, through all the work, science and practice have been held together; the facts of experimental physiology have been and are tested, every inch of the way, by the facts of medicine, surgery, and pathology. The infinite minuteness and complexity of the investigation, and its innumerable side-issues, are past all telling. They who are doing the work, in science and in practice, have always had in their thoughts the fear of fallacies in the interpretation of these highest forms of life. Sir William Gowers, fourteen years ago, wrote as follows of the earlier workers:—

"Doubt was formerly entertained as to the existence of differentiation of function in different parts of the cortex, but recent researches have

established the existence of a differentiation which has almost revolutionised cerebral physiology, and has vastly extended the range of cerebral diagnosis. The first step of the new discovery was constituted by the clinical and pathological observations of Hughlings Jackson, which suggested the existence, on each side of the fissure of Rolando, of special centres for the movements of the leg, arm, and face. These observations led to the experiments of Ferrier, which resulted in the demonstration of the existence in the cortex of the lower animals of well-defined regions, stimulation of which caused separate movements, or evidence of special sense excitation, while the destruction of the same parts caused indications of a loss of the corresponding function. Hence he came to the conclusion that these regions constitute actual motor and sensory centres. Ferrier had, however, been anticipated in many of these results by two German experimenters, Fritsch and Hitzig, whose results, differing a little in detail, correspond closely in their general significance. Many other investigations of the same character have since been made, of which those of Munk are especially important. The original observations of Hughlings Jackson left little doubt that the general facts, learned from experiments on animals, are true of man; and this conclusion has been to a large extent confirmed by pathological and clinical observations directed to the verification on man of the pathological results. To this verification the labours of Charcot and his coadjutors have largely contributed. But the verification has already made it probable that some differences exist between the brain of man and that of higher animals (even of monkeys), and that the conclusions from the latter cannot be simply transferred to the former."

Many and great difficulties, beyond this danger of the fallacy of "simple transference," beset every step of the work: it required the right use of the most delicate and susceptible instruments and tests, and the right understanding of anatomy, microscopic anatomy, comparative anatomy, organic chemistry, electricity, and physics: every moment of advance must be guarded, every word must be weighed. Among the earlier difficulties, was the failure of almost all the physiologists, before Hitzig, to produce muscular action by excitation of the cerebral cortex. Longet, Magendie, Flourens, Matteuci, Van Deen, Weber, Budge, and Schiff, had all failed. Hitzig (*Untersuchungen über das Gehirn*, Berlin, 1874) had observed, in man, that it was easy to produce movements of the eyes by the passage of the constant current through the occipital region.* Taking this fact for a starting-point, he used a very low current, and thereby succeeding in producing certain definitive muscular movements by stimulation of the cortex in animals. Of Hitzig's work, Sir Victor Horsley says:—

"It was not till 1870 that the next absolute proof (after Bell's work in 1813) was obtained of

* That the surface of the brain is not sensitive of such stimulation, that it does not perceive its own substance, was known to Aristotle. The fact is so familiar that there is no need to quote evidence of it, beyond that of Sir Charles Bell, "I have had my finger deep in the anterior lobes of the brain, when the patient, being at the time acutely sensible, and capable of expressing himself, complained only of the integument."

the localisation of function, so far as the highest centres of the nervous system were concerned. In that year Fritsch and Hitzig discovered that electrical excitation, with minimal stimuli, of various points of the cortex, caused those storehouses, of which Willis spoke, to discharge, and to reveal their function by the precise limitation of the groups of muscles which they were able to throw into action. These researches were abundantly confirmed and greatly extended by Professor Ferrier, and thus has been constructed in the history of this subject the most recent great platform or stage of permanent advance." *

Hitzig gives the following summary of his results :—

"A part of the cerebral surface, in the dog, is motor; another part is non-motor.

"The motor part lies, roughly speaking, more anteriorly; the non-motor part lies more posteriorly. By electrical stimulation of the motor part, one obtains combinations of muscular contractions on the opposite side of the body.

"These muscular contractions, by the use of very weak currents, can be localised to certain definite groups of muscles. With stronger currents, which stimulate similar or contiguous regions, other muscles are involved, and even the corresponding muscles of the trunk. The isolated stimulation of a limited group of muscles can only be made possible by the use of very weak currents over very small areas, which we will call centres for the sake of brevity."

* Horsley, *Fullerian Lectures*, 1891, *loc. cit.*

The thirty years since Hitzig's work cannot be put here, for they would take a volume to themselves. There have been, now and again, differences of interpretation of this or that fact, diversities of results, and problems too hard to solve, and other difficulties, such as befall all the natural sciences; but these imperfections amount to very little, when the whole result comes to be reckoned up. The marvel is that the work is so nearly perfect, seeing its immeasurable complexity.

Let any man, who has but touched the study of physiology, consider what is involved in even the most superficial observation of the simplest facts of the nervous system: for instance, the ordinary nerve-muscle preparation that is taught to every medical student, or the microscopic structure of the spinal cord, or the Wallerian method. Or let him consider how the physiology of the nervous system has been founded on the lower forms of life: the work of Romanes and others on the Medusa and the Echinodermata, and Huxley's work in biology, and the endless chain of forces that are alike in man and in jelly-fishes. Then let him try to estimate the output of hard thinking, for the advance from lower to higher structures, and up to man; the vigilant criticism of all theories and foregone conclusions, the incessant self-judgment and wearisome doubts and disputes all the way, elusiveness of facts, and vagueness of words. And the results thus wrung out of science had still to be stated in terms of practice, and tested by the facts of medicine, surgery, and pathology, and used in

every hospital in the civilised world, not only for the saving of life, but also for the diagnosis and medical or surgical treatment of innumerable varieties of disease or injury of the brain, the cord, or the nerves. Sir Michael Foster, in a short summary of the problems of physiology, puts clearly these consummate difficulties of the physiology of the nervous system :—

"In the first place there are what may be called general problems, such as, How the food, after its preparation and elaboration into blood, is built up into the living substance of the several tissues? How the living substance breaks down into the dead waste? How the building up and breaking down differ in the different tissues in such a way that energy is set free in different modes, the muscular tissue contracting, the nervous tissue thrilling with a nervous impulse, the secreting tissue doing chemical work, and the like? To these general questions the answers which we can at present give can hardly be called answers at all.

In the second place there are what may be called special problems, such as, What are the various steps by which the blood is kept replenished with food and oxygen, and kept free from an accumulation of water, and how is the activity of the digestive, respiratory, and excretory organs, which effect this, regulated and adapted to the stress of circumstances? What are the details of the vascular mechanism by which each and every tissue is for ever bathed with fresh blood, and how is that working delicately adapted to all the varied changes of the body? And, *compared with which all other*

problems are insignificant and preparatory only, how do nervous impulses so flit to and fro within the nervous system as to issue in the movements which make up what we sometimes call the life of man?"

The physiology of the nervous system is wrought to finer issues now than in the time of Bell and Magendie; and this generation of students may live to see the present facts and methods of cerebral localisation as the mere rudiments or elements of science. Happily for mankind, science has already so far elucidated them that they have done good service for the diagnosis and treatment of disease, and for the saving of lives.

Some examples have been given, in the foregoing chapters, of the value of physiological experiments on animals. It would be easy to lengthen the list, for there is no general subject in all physiology that does not owe something to this method: as Mr Darwin said, in his evidence before the Royal Commission of 1875, "I am fully convinced that physiology can progress only by the aid of experiments on living animals. I cannot think of any one step which has been made in physiology

without that aid." Many examples have been left out altogether — the work of Boyle, Hunter, Lavoisier, Haldane, Despretz, and Regnault, on animal heat and on respiration; of Petit, Dupuy, Breschet, and Reid, on the sympathetic system; of Galvani, Volta, Haller, du Bois-Reymond, and Pflüger, on muscular contractility: nothing has been said of the work lately done on the suprarenal glands and "adrenalin," and on the blood-pressure in its relation to secretion. For the most part, only those examples have been taken that occur far back in the history of physiology: more has been said about the past than about the present. First, because it was necessary to put an end to the false statements that are made, by those who are opposed to all experiments on animals, about the work done in the past. Next, because the abstruse details of physiology, in the present, are not intelligible for general reading. Next, because it is impossible now to isolate physiology, or to say what belongs to physiology alone, to have back the simpler problems of the past, to discover the circulation of the blood twice. But the experimental method, alike in the past and in the present, has been the chief way of advance. And if a forecast may be made without offence, it is certain that the work of physiology, as in the past and the present, so in the near future, will exercise a profound influence for good on medical and surgical treatment. Among the subjects that especially occupy physiologists now are, the more exact localisation and interpretation of the special sense-centres, and the

better knowledge of the internal secretions and chemical influences of the glands and tissues of the body. It would be hard to find two fields of work more sure to favour the growth of the *arbor vitæ* side by side with the *arbor scientiæ*.

PART II

EXPERIMENTS IN PATHOLOGY, MATERIA MEDICA, AND THERAPEUTICS

I

INFLAMMATION, SUPPURATION, AND BLOOD-POISONING

PATHOLOGY, the study of the causes and products of diseases, is a younger science than physiology: the use of the microscope was the beginning of pathology; and the microscope, even so late as sixty years ago, was very different to the microscope now. The great pathologists of that time had not the lenses, microtomes, and reagents that are now in daily employment; they knew nothing of the present methods of section-cutting and differential straining. But the publication in 1839 of Schwann's cell-theory marks the rise of modern pathology. In 1843, Darwin wrote his first draft of the doctrine of the origin of species; and Pasteur, that year, was in for his examination at the École Normale. The work of Schwann, Virchow, and Pasteur had such profound influences on science that the span of sixty years seems to cover the modern development of pathology: and this span of years is marked, half-way, by the rise of bacteriology. In 1875, when the Royal Commission on Experiments on Animals was held in

London, the evidence was concerned practically with physiology alone: very little was said about pathology, and of bacteriology hardly a word. The witnesses say that they "believe they are beginning to get an idea" of the true nature of tubercle: and the evidence as to the nature of anthrax, given by Sir John Simon, reads now like a very old prophecy:—

"We are going through a progressive work that has many stages, and are now getting more precise knowledge of the contagium. By these experiments on sheep it has been made quite clear that the contagium of sheep-pox is *something of which the habits can be studied, as the habits of a fern or a moss can be studied: and we look forward to opportunities of thus studying the contagium outside the body which it infects. This is not a thing to be done in a day, or perhaps in ten years, but must extend over a long period of time.* Dr Klein's present paper represents one very important stage of a vast special study. He gives the identification of the contagium as *something which he has studied to the end in the infected body, and which can now in a future stage be studied outside the body.*"

Thirty years ago, there was no bacteriology, in the present sense of the word: and now the "habits" of these "contagia" have been studied, outside and inside the body, with amazing accuracy. It has been proved, past all possibility of doubt, that the pathogenic bacteria are the cause of infective diseases; they have fulfilled Koch's postulates —that they should be found in the diseased tissues,

be cultivated outside the body, reproduce the same disease in animals, and be found again in the tissues of those animals. By an immeasurable amount of hard work crowded into a few years, this New World of bacteriology has been subdued. The Royal Commissioners of 1875, speaking of physiological experiments only, said, "It would require a voluminous treatise to exhibit in a consecutive statement the benefits that medicine and surgery have derived from these discoveries." If physiology in 1875 required a treatise, bacteriology in 1902 requires a shelf: and it is impossible here to give more than the faintest outline of some of the work that has been done.

But all pathology is not bacteriology; and it would take a treatise of prodigious length to set forth the work of modern pathology in the years before anything was known of bacteria. The microscopic structure of tumours and of all forms of malignant disease, the nature of amyloid, fatty, and other degenerative changes, and the chief facts of general pathology—hypertrophy and atrophy, necrosis, gangrene, embolism, and many more—all these subjects were studied to good purpose, before bacteriology. Above all, men were occupied in the study of inflammation under the microscope. It was this use of the microscope that revolutionised pathology; especially, it made visible the whole process of inflammation, the most minute changes in the affected tissues, the slowing and arrest of the blood in the capillaries, the choking-up of the stream, and the escape of blood-cells out of the

capillaries into the tissues. Everything had been made ready for the fuller interpretation that was coming from bacteriology: the old naked-eye descriptions of inflammation were left behind; men set aside the definition of Celsus, that it was *rubor et tumor cum calore et dolore*—words that sound like Molière's jest about the *vis dormitiva* of opium—they watched inflammation under the microscope, in such transparent structures as the frog's web and mesentery, the bat's wing, and the tadpole's tail. It was thus that Wharton Jones discovered the rhythmical contraction of the veins in the bat's wing. The discovery of the escape of the white blood-cells, *diapedesis*, through the walls of the capillaries, was made by Waller and Cohnheim. To those who are opposed to all experiments on animals, it may seem a very small thing that a blood-cell should be on one side or the other of a microscopic film in a tadpole's tail; but this *diapedesis*, the first move of the blood in its fight against disease, is now seen, in the light of Metschnikoff's work, as a fact of very great importance.

The history of this transitional period, from the study of inflammation in transparent living tissues to the use, in surgery, of the facts of bacteriology, is told in Lord Lister's Huxley Lecture, October 1900. He describes how the foundations were laid in surgical pathology, by microscopical and experimental work on inflammation, coagulation, suppuration, and pyæmia, for bacteriology to build on: how his own share of the work began when he was house-surgeon to Sir John Erichsen at University

College Hospital, and afterward to Mr Syme in Edinburgh, and how it was continued through all his Edinburgh and Glasgow life :—

"After being appointed to the Chair of Surgery in the University of Glasgow, I became one of the surgeons to the Royal Infirmary of that city. Here I had, too, ample opportunities for studying hospital diseases, of which the most fearful was pyæmia. About this time I saw the opinion expressed by a high authority in pathology that the pus in a pyæmic vein was probably a collection of leucocytes. Facts such as those which I mentioned as having aroused my interest in my student days in a case of pyæmia, made such a view to me incredible; and I determined to ascertain, if possible, the real state of things by experiment. . . .

"While these investigations into the nature of pyæmia were proceeding, I was doing my utmost against that deadly scourge. Professor Polli, of Milan, having recommended the internal administration of sulphite of potash on account of its antiputrescent properties, I gave that drug a very full trial as a prophylactic. . . . At the same time, I did my best, by local measures, to diminish the risk of communicating contagion from one wound to another. I freely employed antiseptic washes, and I had on the tables of my wards piles of clean towels to be used for drying my hands and those of my assistants after washing them, as I insisted should invariably be done in passing from one dressing to another. But all my efforts proved abortive; as I could hardly wonder when I believed, with chemists generally, that putrefaction was caused by the oxygen of the air.

"It will thus be seen that I was prepared to

welcome Pasteur's demonstration that putrefaction, like other true fermentations, is caused by microbes growing in the putrescible substance. Thus was presented a new problem: not to exclude oxygen from the wounds, which was impossible, but to protect them from the living causes of decomposition by means which should act with as little disturbance of the tissues as is consistent with the attainment of the essential object. . . . To apply that principle, so as to ensure the greatest safety with the least attendant disadvantage, has been my chief life-work." *

And, of course, the application of that principle is not limited to the performance of the major operations of surgery. It is in daily use in every hospital, and in every practice all the world over, for the safe and quick healing of whole legions of injuries, "casualties," and minor operations.

But what of Semmelweis, and his study of puerperal fever? Did he not, before Lord Lister, and without the help of experiments on animals, discover antiseptic surgery? His claim is urged by those who are opposed to all such experiments. And the answer is, that his work was lost just for want of experiments on animals. If he could have demonstrated, as Pasteur did, the living organism, the thing itself, there in the tissues of an infected rabbit, and in a test-tube, and under a microscope, he might have stopped the mouths of his adversaries. He could not. He could only demonstrate

* See also the admirable Life of Pasteur, by M. Valléry-Radot. Translation by Mrs Devonshire, vol. ii., p. 20.

to them the fact that their patients died, and his patients lived: and that some sort of direct infection was the cause of the deaths. The tragedy of his life cannot be told too often, and may be told again here.* For want of the final proof that bacteriology, and the inoculation of animals, alone could give, he was unable to hold out against his enemies till Pasteur could rescue him.

In 1846, when he was twenty-three years old, Ignaz Semmelweis was appointed assistant-professor in the maternity department of the huge general hospital of Vienna. For many years, the mortality in the lying-in wards had been about 1.25 per cent., and no more. Then, under a new professor, it had risen; and, for some years before Semmelweis came on the scene, it had been 5 per cent., or even 7 per cent. In October 1841, there had been an epidemic that had lasted till May 1843. In these twenty months, out of 5139 women delivered, 829 had died; that is to say, 16 per cent.

There were two sets of wards in the maternity department. The one set may be called Clinique A, and the other Clinique B. For many years, the mortality had been the same in each. In 1841 a change was made: Clinique A was assigned to the teaching of students, and Clinique B to the teaching of midwives: and, so soon as this change had been made, the mortality in Clinique B became less, but

* This account of Semmelweis, reprinted by permission from the *Middlesex Hospital Journal*, is mostly taken from Dr Theodore Duka's excellent paper on "Childbed Fever." (*Lancet*, 1886.)

the mortality in Clinique A did not. Commissions of inquiry were held, and in vain. It was suggested that the foreign students were somehow to blame, nobody knew why; and many of them were sent away. Still the deaths went on. Women admitted to Clinique A would go down on their knees and pray to be allowed to go home; almost every day the bell was heard ringing in the wards, for the administration of the Sacrament to a dying woman. People talked about atmospheric influences, and overcrowding, and the tainted air of old wards, and the power of the mind over the body: and Semmelweis set to work.

He observed that cases of protracted labour in Clinique A died, almost all of them; but not in Clinique B. He observed also that cases of premature labour, nearly all of them, did well, whichever Clinique they were in; so did those women who were delivered before they came to the hospital, and were admitted after delivery. He observed also that a row of patients, lying side by side, would all be attacked at once in Clinique A; which never happened in Clinique B. He tried everything: he altered the details of treatment; he used various subterfuges to prevent one of the professors from examining serious cases; he enforced this or that rule in Clinique A, because it was the custom in Clinique B; he slaved away at the notes of the cases—and at last the truth came to him, by the death of one of his friends from a dissection-wound. He says, "My friend's fatal symptoms unveiled to my mind an identity with those which I had so

often noticed at the deathbeds of puerperal cases." He saw now that the students, coming straight from the dissecting-rooms, had infected the patients during examination.

In May 1847 he gave orders that every student, before examining, should thoroughly disinfect his hands. But, though he had reckoned with dissecting-room poisons, he had forgotten to reckon with other sources of infection. In October of that year, a woman was admitted who had malignant disease; of twelve women examined after her, eleven got puerperal fever, and died. In November, a woman was admitted who had a suppurating knee-joint, with sinuses; and eight women were infected from her, and died. Therefore Semmelweis said, "Not only can the particles from dead bodies generate puerperal fever, but any decomposed material from the living body can also generate it, and so can air contaminated by such materials." Henceforth he isolated all infected cases, he enforced the strict use of disinfectants: and the mortality in Clinique A, which in May 1847 had stood at 12.24 per cent., fell in December to 3.04, and in 1848 was 1.27.

His work was taken up with enthusiasm by Hebra, Skoda, and Haller; the news of it was sent to every capital in Europe. In February 1849 Haller read a paper on it before the Medical Society of Vienna, and said, "The importance of these observations is above all calculation, *both for the maternity department and for the hospitals in general, but particularly for the surgical wards.*" A committee was nominated to report on the whole

matter; but it was opposed by the professor in charge of Clinique A, and nothing came of it. In May 1850, Semmelweis opened a great debate on puerperal fever, which occupied three sittings of the Vienna Medical Society. His opponents were there in full force, all the Scribes and Pharisees of the profession. They brought about a vague distrust of his figures and his facts; they got people to believe that there must be "something else" in puerperal fever, as well as the local infection. Semmelweis began to be discouraged. The University authorities made a dead set against him —they refused to renew his appointment, they got him out of the hospital, and out of Vienna. He went to Pesth, and was Professor of Midwifery there; but the same opposition and hostility were at Pesth as at Vienna. Slowly he began to lose his hold over himself, went down hill, became excitable and odd. The end came in July 1865. At a meeting of University professors, he suddenly took a paper from his pocket and read aloud to them a solemn oath, to be enforced on every midwife and every doctor. His mind had given way: he was moved to an asylum at Vienna, and died there a few weeks later. He was only forty-two when he died—*What a wounded name, Things standing thus unknown, shall live behind me.*

The contrast between the work of Semmelweis and the work of Pasteur cuts like a knife here. The failure of Semmelweis' teaching may be estimated by the fact that it had all to be done over again. The year of his success at Vienna was

1848. Eight years later, in the Paris Maternity Hospital, between 1st April and 10th May 1856, came such an outbreak of puerperal fever that out of 347 patients 64 died. In 1864, out of 1350 cases, 310 deaths. In Jan.-Feb. 1866, out of 103 cases, 28 deaths: "Women of the lower classes looked upon the Maternité as the vestibule of death." In 1877-78, came the use of carbolic acid and perchloride of mercury at the hospital, thirty years after Semmelweis' work: and, about the same time, Pasteur's discovery of the streptococcus in puerperal fever.* Pasteur could demonstrate to his opponents the visible cause of the infection, the thing itself; Roux tells the story:—

"Dans le pus des abcès chauds et dans celui des furoncles on constate un petit organisme arrondi, disposé en amas, qu'on cultive facilement dans le bouillon. On le retrouve dans l'ostéomyélite infectieuse des enfants. Pasteur affirme que l'ostéomyélite et le furoncle sont deux formes d'une même maladie, et que l'ostéomyélite est le furoncle de l'os. En 1878, cette assertion a fait rire bien les chirurgiens.

Dans les infections puerpérales, les caillots renferment un microbe à grains arrondis se disposant en files. Cet aspect en chapelet est surtout manifesté dans les cultures. Pasteur n'hésite pas à déclarer que cet organisme microscopique est la cause la plus fréquente des infections chez les femmes accouchées. Un jour, dans une discussion sur la fièvre puerpérale à l'Académie de Médicine, un de ses collégues le plus écoutés dissertait éloquemment

* See Pasteur's Life, vol. ii., p. 89.

sur les causes des épidémies dans les maternités. Pasteur l'interrompt de sa place: *Ce qui cause l'épidémie, ce n'est rien de tout cela: c'est le médecin et son personnel qui transportent le microbe d'une femme malade à une femme saine.* Et comme l'orateur répondit qu'il craignait fort qu'on ne trouve jamais ce microbe, Pasteur s'élance vers le tableau noir, dessine l'organisme en chapelet de grains, en disant, *Tenez, voici sa figure.*" (Roux, *L'Œuvre Médicale de Pasteur. Agenda du Chimiste*, 1896, p. 528.)

All suppuration, and all forms of "blood-poisoning"—abscesses, boils, carbuncles, erysipelas, puerperal fever, septicæmia, pyæmia—are due to minute organisms, various kinds of *micrococcus.* It has indeed been shown that suppuration may, in exceptional conditions, occur without micro-organisms: but practically every case of suppuration is a case of infection either from without or from within the body. There is no room here for any account of the work spent on these micrococci: on their identification, isolation, culture, and inoculation. It is the same with all the pathogenic bacteria—each kind has its own habits, phases and idiosyncrasies, antagonisms and preferences: nothing is left unstudied—the influences of air, light, heat, and chemistry; all the facts of their growth, division, range of variation, grades of virulence, vitality, and products; the entire life and death of each species, and everything that it is, and does, and can be made to do:—

"Doubtless immense progress has been made

during the last two or three decades, but a vast amount still remains to be done. We have only touched the fringe of the explanation of the difficult problems of immunity, of the extraordinary variations in virulence and effects of the same organism, and of the important question of cure in, and prevention of, infective diseases; while the chemistry of the products of bacterial activity is but in its infancy." (Hewlett, *Manual of Bacteriology*, 1898.)

The difficulties of bacteriology are written across every page of the text-books: above all, the difficulties of attenuating or intensifying the virulence of bacteria, and of immunising animals, and of procuring from them an immunising serum of exact and constant strength. Every antitoxin is the outcome of an immeasurable expenditure of hard international work, unsurpassed in all science for the fineness of its methods and the closeness of its arguments.

It has been said, by those who are opposed to all experiments on animals, that the virtue of all antitoxins is due to the carbolic acid mixed with some of them. They give the following wonderful explanation in one of their journals:—

"We are often asked if there is any germ of truth at all in the serum treatment of disease. There is; and it is as well that our readers should know exactly what it is. In infectious diseases, a proportion of the delicate blood-corpuscles die and become waste matter in the blood. If the patient be of good constitution, his system soon eliminates this dead matter. Now, all serums being very

liable to decomposition, are preserved by a small proportion of carbolic acid, and this being injected hypodermically acts antiseptically in the blood, and so assists nature in getting rid of the decomposing corpuscles."

As Ambroise Paré said of the spells and magic of his time, *It is pleasant to know this way of practising medicine.*

The older theories of disease had attributed infection to the intemperature of the weather, the powers of the air, or the work of the devil; later, men recognised that there must be a *materies morbi*, something particular, transmissible, and perhaps alive, but it was still a "nameless something." Therefore, they overestimated the constitutional, personal aspect of a case of infective disease, against the plain evidence of case-to-case infection or inoculation: they studied with infinite care and minuteness the weather, the environment, the family history, the previous illnesses of the patient—everything, except the immediate cause of the trouble. But modern pathology, like Pasteur, says, *Tenez, voici sa figure.*

The antiseptic method was based on bacteriology, resting as it did on the proof afforded by Pasteur that putrefaction was caused by bacteria, and not by the oxygen of the air, as had been previously believed. If any man would measure one very small part of the lives that are saved by this method, let him contrast the treatment of empyema fifty years ago with its treatment now. If he would measure the saving, not of lives but of limbs, let

him take the treatment of compound fractures. If he would measure the saving of patients from pain, fever, and long confinement to bed, let him take the ordinary run of surgical cases, not only the major operations but all abscesses, lacerated wounds, foul sores, and so forth.

A serum has also been used of late years for the treatment of micrococcus-infection, and has given good results in many cases. It has been used, also, to avert the risk of such infection in certain operations where the antiseptic method cannot be strictly carried out.

II

ANTHRAX

IN animals, anthrax is also called *charbon*, splenic fever, or splenic apoplexy: in man, the name of *malignant pustule* is given to the sore at the point of accidental inoculation, and the name of *wool-sorter's disease* is given to those cases of anthrax where the lungs are infected by inhalation of the spores of the *bacillus anthracis*. The disease occurs among hide-dressers, woolsorters, brushmakers, and rag-pickers: among animals, it occurs in sheep, cattle, horses, and swine:—

"Many of the outbreaks of anthrax in England have been in the neighbourhood of Bradford, and have been traced to the use of infected wool-refuse as manure. A map published by the Board of Agriculture shows that the outbreaks of anthrax are most frequent in those counties of Great Britain where dry foreign wools, hairs, hides, and skins are manufactured into goods. In 1892, there were forty-two outbreaks of anthrax in the West Riding of Yorkshire, as against two in the North Riding, and one in the East Riding. An undoubted fact in connection with anthrax is its tendency to recur on certain farms. During 1895, the disease

reappeared on twenty-three farms or other premises in England, and six in Scotland, where it had been reported in the previous year." (Dr Poore's Milroy Lectures, *On the Earth in relation to Contagia*, 1899.)

An admirable account of the disease, as it occurs in man, is given by Dr Hamer and Dr Bell, in the valuable series of monographs lately edited by Dr Oliver of Newcastle, under the title *Dangerous Trades* (London, John Murray, 1902). Happily, the disease is very rare among men, even among those most exposed to it. For its treatment in man, an antitoxin has been used with some success: but the cases are too few to be of importance.

The *bacillus anthracis* was first seen more than fifty years ago: "Anthrax has the distinction of being the first infectious disease the bacterial nature of which was definitely proven." * Pollender in 1844, Roger and Davaine in 1850, noted the *petits bâtonnets* in the blood of sheep dead of the disease, and thought they were some sort of microscopic blood-crystals: it was not till 1863, after Pasteur's study of lactic-acid fermentation, that Davaine realised they were living organisms. Afterward, Koch succeeded in making cultures of them, and reproduced the disease by inoculating animals with these cultures; yet it was said, so late as 1876, that the bacillus anthracis was not the cause of anthrax, but only the sign of it:

* See Dr Flexner's account of the disease, in volume xix. of Stedman's *Twentieth Century Practice*.

"Along with the bacilli, there are blood-cells and blood-plasma, and these contain the true amorphous virus of anthrax." Then came Pasteur's work, and reached its end in the experiments at Chartres, and the famous test-inoculations (1881) at Pouilly-le-Fort.

In the *Agenda du Chimiste* (1896) M. Roux gives the following account of this work, which he watched from first to last:—

"Vaccination against *charbon* has now been put to the test of practice for fourteen years. Wherever it is adopted, there the losses from *charbon* have become insignificant. It was followed by vaccination against swine-measles, *rouget des porcs*, the special study of our poor friend Thuillier. But the immediate result of Pasteur's vaccinations is their least merit: they have given men absolute faith in a science that could show such good works, they have started a movement that is irresistible; above all, they have set going the whole study of immunity, which is bringing us at last to a right way of treating infective diseases.

"Virulence is a quality that microbes can lose, or can acquire. Suppose we came across the anthrax-bacillus so far attenuated, in the way of Nature, that it had lost all power to kill—of course we should fail to recognise it; we should take it for an ordinary bacillus of putrefaction: you must watch it through each phase of its attenuation, to know that the harmless organism is the descendant of the fatal virus. But you can give back to it the virulence that it has lost, if you put it, to begin with, under the skin of a very delicate subject, a mouse only one day old. With the blood of this

mouse inoculate another, a little older, and it will die. Passing by this method from younger to older mice, we come to kill adult mice, guinea-pigs, then rabbits, then sheep, etc. Thus, by transmission, the virus gains strength as it goes. Doubtless this increase of virulence, that we bring about by experiment, occurs also in Nature; and it is easy to see how a microbe, usually harmless to this or that species of animals, might become deadly to it. Is not this the way that infective diseases have appeared on the earth from age to age?

"*See how far we have come, from the old metaphysical ideas about virulence, to these microbes that we can turn this way or that way—stuff so plastic that a man can work on it, and fashion it as he likes.*"

Pasteur's note on the attenuation of anthrax was presented to the Académie des Sciences on 28th February 1881; and the test-inoculations at Pouilly-le-Fort were made in May of that year. It was hardly to be expected that every country, in every year, should obtain such results as France now takes as a matter of course; and at one time, about eighteen years ago, there was in Hungary a "conscientious objection" to the inoculation of herds against the disease. In Italy, from 1st May 1897 to 30th April 1898, the issue of anti-charbon vaccine from one institute alone, the Sero-Therapeutic Institute at Milan, was 165,000 tubes, enough to inoculate 33,734 cattle and 98,792 sheep. And in France, between 1882 and 1893, more than three million sheep, and nearly half a million cattle, were inoculated.

The work done in France was published by M. Chamberland, in the *Annales de L'Institut Pasteur*, March 1894. The following translation of his memoir—*Résultats pratiques des Vaccinations contre le Charbon et le Rouget en France*—shows something of the national influence of the Pasteur Institute :—

1. *Charbon.*

"After the famous experiments at Pouilly-le-Fort, MM. Pasteur and Roux entrusted to me the whole method and practice of the vaccinations against *charbon.* Twelve years have passed, and it is now time to put together the results, and to make a final estimate of the value of these preventive inoculations.

"Every year we ask the veterinary surgeons to report—

1. The number of animals they have vaccinated.
2. The number that have died after the first vaccination.
3. The number that have died after the second vaccination, within the twelve days following it.
4. The number that have died during the rest of the year.
5. The average annual mortality before the practice of vaccination.

"The sum total of all the reports is given in the following tables :—

Vaccination against Charbon (France).

Sheep.

Years.	Total Number of Animals Vaccinated.	Number of Reports.	Animals Vaccinated according to Reports received.	Mortality. After First Vaccination.	Mortality. After Second Vaccination.	Mortality. During the rest of the Year.	Total.	Total loss per 100.	Average loss before Vaccination.
1882	270,040	112	243,199	756	847	1037	2,640	1.08	10%
1883	268,505	103	193,119	436	272	784	1,492	0.77	,,
1884	316,553	109	231,693	770	444	1033	2,247	0.97	,,
1885	342,040	144	280,107	884	735	990	2,609	0.93	,,
1886	313,288	88	202,064	652	303	514	1,469	0.72	,,
1887	293,572	107	187,811	718	737	968	2,423	1.29	,,
1888	269,574	50	101,834	149	181	300	630	0.62	,,
1889	239,974	43	88,483	238	285	501	1,024	1.16	,,
1890	223,611	69	69,865	331	261	244	836	1.20	,,
1891	218,629	65	53,640	181	102	77	360	0.67	,,
1892	259,696	70	63,125	319	183	126	628	0.99	,,
1893	281,333	30	73,939	234	56	224	514	0.69	,,
Total	3,296,815	990	1,788,879	5668	4406	6798	16,872	0.94	10%

Cattle.

Years.	Total Number of Animals Vaccinated.	Number of Reports.	Animals Vaccinated according to Reports received.	Mortality. After First Vaccination.	Mortality. After Second Vaccination.	Mortality. During the rest of the Year.	Total.	Total loss per 100.	Average loss before Vaccination.
1882	35,654	127	22,916	22	12	48	82	0.35	5%
1883	26,453	130	20,501	17	1	46	64	0.31	,,
1884	33,900	139	22,616	20	13	52	85	0.37	,,
1885	34,000	192	21,073	32	8	67	107	0.50	,,
1886	39,154	135	22,113	18	7	39	64	0.29	,,
1887	48,484	148	28,083	23	18	68	109	0.39	,,
1888	34,464	61	10,920	8	4	35	47	0.43	,,
1889	32,251	68	11,610	14	7	31	52	0.45	,,
1890	33,965	71	11,057	5	4	14	23	0.21	,,
1891	40,736	68	10,476	6	4	4	14	0.13	,,
1892	41,609	71	9,757	8	3	15	26	0.26	,,
1893	38,154	45	9,840	4	1	13	18	0.18	,,
Total	438,824	1255	200,962	177	82	432	691	0.34	5%

"Comparing the figures in the fourth column with those in the second, we see that a certain number of veterinary surgeons neglect to send their reports at the end of the year. The number of reports that come to us even tends to get less each year. The fact is, that many veterinary surgeons who do vaccinations every year content themselves with writing, 'The results are always very good; it is useless to send you reports that are always the same.'

"We have every reason to believe, as a matter of fact, that those who send no reports are satisfied; for if anything goes wrong with the herds, they do not fail to let us know it at once by special letters.

"Anyhow, thanks chiefly to new veterinary surgeons who do send reports, we see that in the twelve years, up to 1st January of this year, we have had exact returns as to 1,788,879 sheep and 200,962 cattle—about half of all those that were vaccinated.

"The mortality among sheep and cattle is slightly higher after the first vaccination than after the second. This fact seems to us easy to explain. The animals reported dead include both those that died as the result of the vaccinations, and those that, being already infected at the time, died of the actual disease. But, at the time of second vaccination, the animals are already more or less protected: hence a lower mortality from the actual disease, and a lower sum total.

"The whole loss of sheep is about 1 per cent.:

the average for the twelve years is 0.94. So we may say that *the whole average loss of vaccinated sheep, whether from vaccination or from the disease itself, is about* 1 *per cent.* The loss of vaccinated cattle is still less: for the period of twelve years, it is 0.34, or about ⅓ per cent.

"These results are extremely satisfactory. It is to be noted especially that the average annual death-rate from *charbon*, before vaccination — the average given in these reports—is estimated at 10 per cent. among sheep, and 5 per cent. among cattle. But even if we put it at 6 per cent. for sheep, and 3½ per cent. for cattle, and say that the worth of a sheep is 30 francs, and of an ox or a cow 150 francs—which is well below their real value—even then it is obvious that the advantage of these vaccinations to French agriculture is about five million francs in sheep, and two million in cattle. And these figures are rather too low than too high.

2. *Rouget.*

"Some years after the discovery of vaccination against *charbon*, M. Pasteur discovered the vaccine for a disease of swine known under the name of *rouget*. From 1886, these vaccines were prepared and sent out under the same conditions as the vaccines against *charbon*. The following table gives the reports that have come to us of this disease: *—

* "The reports for 1893 are at present too few to be utilised for this table."

VACCINATION AGAINST ROUGET (FRANCE).

Years.	Total Number of Animals Vaccinated.	Number of Reports.	Animals Vaccinated according to Reports received.	Mortality. After First Vaccination.	Mortality. After Second Vaccination.	Mortality. During the rest of the Year.	Total.	Total loss per 100.	Average loss before Vaccination.
1886	For these two years France and other countries are put together.	49	7,087	91	24	56	171	2.41	20%
1887		49	7,467	57	10	23	90	1.21	„
1888	15,958	31	6,968	31	25	38	94	1.35	„
1889	19,338	41	11,257	92	12	40	144	1.28	„
1890	17,658	41	14,992	118	64	72	254	1.70	„
1891	20,583	47	17,556	102	34	70	206	1.17	„
1892	37,900	38	10,128	43	19	46	108	1.07	„
Total	111,437	296	75,455	534	188	345	1067	1.45	20%

"*The total average of losses during the past seven years is* 1.45 *per cent., or about* 1½ *per cent.*

"This average is appreciably higher than the average for *charbon.* But it must be noted that the mortality from *rouget* among swine, before vaccination, was much higher than that from *charbon* among sheep. It was about 20 per cent.; a certain number of reports speak of losses of 60 and even 80 per cent.: so that almost all the veterinary surgeons are loud in their praises of the new vaccination."

The rest of M. Chamberland's paper is concerned with the defects, such as they are, of the vaccinations, and the need of absolute cleanliness in the making of them: which is somewhat difficult

for this vast number of vaccinations of animals all over France, and in other parts of the world. The whole story of the discovery is told in M. Valléry-Radot's Life of Pasteur: and the whole story of *rouget*, in the same most fascinating book, vol. ii., p. 180.

III

TUBERCLE

BEFORE Laennec, tubercle had been taken for a degenerative change of the tissues, much like other forms of degeneration. It was Laennec who brought men to see that it is a disease of itself, different from anything else; and this great discovery of the specific nature of tubercle, and his invention of the stethoscope, place him almost level with Harvey. He founded the facts of tubercle, and on that foundation Villemin built. In 1865, Villemin communicated to the Académie des Sciences his discovery that tubercle is an infective disease; that he had produced it in rabbits, by inoculating them with tuberculous matter. *En voici les preuves*, he said. He appealed to these inoculations to prove his teaching:—

La tuberculose est une affection spécifique.
Sa cause réside dans un agent inoculable.
L'inoculation se fait très-bien de l'homme au lapin.
La tuberculose appartient donc à la classe des maladies virulentes.

It was no new thing to say, or to guess, that

phthisis was or might be infective. So far back as 1500, Frascatorius had said that phthisis came "by the gliding of the corrupt and noisome humours of the patient into the lungs of a healthy man." Surely, if clinical experience could suffice, men would have made something out of this wisdom of Frascatorius. They made nothing of it; they waited three centuries for Villemin to inoculate the rabbits, and then the thing was done—*En voici les preuves.* Three years later, Chauveau produced the disease in animals, not by inoculation, but by the admixture of tuberculous matter with their food. Then, as the work grew, there came a short period of uncertainty: different species of animals are so widely different in their susceptibility to the disease that the results of further inoculations seemed to go against Villemin; and it was not till 1880 that Cohnheim finally established Villemin's teaching, and even went beyond it, making inoculation the very proof of tubercle:—

"Everything is tuberculous, that can produce tuberculous disease by inoculation in animals that are susceptible to that disease: and nothing is tuberculous, that cannot do this."

Then, in 1881, came the welcome news that Koch had discovered the bacillus of tubercle. In his first published account of it (24th March 1882) he says:—

"Henceforth, in our warfare against this fearful scourge of our race, we have to reckon not with a nameless something, but with a definite parasite,

whose conditions of life are for the most part already known, and can be further studied. . . . Before all things, we must shut off the sources of the infection, so far as it is in the power of man to do this." *

In November 1890 he announced, in the *Deutsche Medizinische Wochenschrift*, the discovery of tuberculin. Its failure was one of the world's tragedies; and, for all the years of careful work that have been given to its improvement, from 1890 until now, it still, in the general opinion of medical men, fails to fulfil the hope that it first inspired. The modified forms of it have given, here or there, good results: the defeat may not be final, and men may live to see phthisis fought and beaten with its own weapons: but, for the present, it is more to the purpose to consider what other benefits have been gained, from the discovery of the tubercle-bacillus in 1882, in every civilised country in the world.

1. It has given to everybody a more reasonable and hopeful view of phthisis and the diseases allied to it. The older doctrine of heredity, that the child inherits the disease itself, has given way to the doctrine that the inheritance, in the vast majority of

* "In Zukunft wird man es im Kampf gegen diese schreckliche Plage des Menschengeschlechtes nicht mehr mit einem unbestimmten Etwas, sondern mit einem fassbaren Parasiten zu thun haben, dessen Lebensbedingungen zum grössten Theil bekannt sind und noch weiter erforscht werden. Es müssen vor allen Dingen die Quellen, aus denen der Infections-stoff fliesst, so weit es in menschlichen Macht liegt, verschlossen werden."

cases, is not that of the disease itself, but that of a tendency or increased susceptibility to the disease.

2. It has brought about an immense improvement in the early and accurate diagnosis of all cases. The bacillus found in the sputa, or in the discharges, or in a particle of tissue, is evidence that the case is tuberculous.

3. It has given evidence, which till 1901 was hardly called in question, that *tabes mesenterica*, a tuberculous disease which kills thousands of children every year, is due in many cases to infection from the milk of tuberculous cows. In England alone, in 1895, the number of children who died of this disease was 7389, of whom 3855 were under one year old.

4. It has proved, and has taught everybody to see the proof, that the sputa of phthisical patients are the chief cause of the dissemination of the disease. By insisting on this fact, it has profoundly influenced the nursing and the home-care of phthisical patients; and it has begun to influence public opinion in favour of some sort of notification of the disease, and in favour of enforcing a law against spitting in public places and conveyances. In some of the principal cities of the United States, laws on this subject have already been enacted.

5. It has greatly helped to bring about the present rigorous control of the meat and milk trades. The following paragraph, taken almost at random, will suffice here:—

"Bacteriological examinations during the past year have shown that more milks are tuberculosis-

infected than is generally supposed, and the importance of carefully supervising milk supplies is becoming more and more acknowledged. Veterinary surgeons are practically agreed that tuberculin is a reliable and safe test for diagnosing the presence of tuberculosis in animals, but affords no index of the extent or degree of the disease. The test, however, will not produce tuberculosis in healthy animals, and has no deleterious effect upon the general health of the animals. The London County Council have decided that all cows in London cowsheds shall be inspected by a veterinary surgeon regularly once in every three months, and that a systematic bacteriological examination shall be conducted of milks collected from purveyors." (*Medical Annual*, 1901.)

6. Tuberculin has come into general use for the detection of tuberculosis in cattle, to "shut off the sources of the infection." A full account of this method in different countries was given by Professor Bang, of Copenhagen, at the Fourth Congress on Tuberculosis, Paris, 1898. The injection of tuberculin is followed in eight to twelve hours by a well-marked rise of temperature, if the animal be tuberculous. Of this test, Professor McFadyean, Principal of the Royal Veterinary College, London, says:—

"I have no hesitation in saying that, taking full account of its imperfection, tuberculin is the most valuable means of diagnosis in tuberculosis that we possess. . . . I have most implicit faith in it, when it is used on animals standing in their own premises and undisturbed. It is not reliable when used in

animals in a market or slaughter-house. A considerable number of errors at first were found when I examined animals in slaughter-houses after they had been conveyed there by rail, etc. Since that, using it on animals in their own premises, I have found that it is practically infallible. I have notes of one particular case, where twenty-five animals in one dairy were tested, and afterwards all were killed. There was only one animal which did not react, and it was the only animal not found to be tuberculous when killed." (Professor McFadyean.)

Two instances of the validity of this test will suffice. In 1899, it was applied to 270 cows on some farms in Lancashire. Of these cows, 180 reacted to the test, 85 did not react, and 5 were doubtful. Tuberculous disease was actually found, when they were killed, in 175 out of the 180=97.2 per cent. (*Lancet*, 5th August 1899). In 1901, Arloing and Courmont published a critical account of the whole subject, and gave the following facts. In 80 calves, which on examination after death were found not tuberculous, the test was negative: in 70 older cattle, which were tuberculous, the test was positive in every case but one, though the dilution of the serum was 1 in 10.* It would be easy to add instances of the value of this test, for it is practised far and wide over the world.

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* For references to this paper, and to evidence put forward against the validity of the test, and for criticism of such evidence, see Gould's *Year-Book of Medicine and Surgery*, 1902 (Philadelphia, W. B. Saunders & Company).

At the British Congress on Tuberculosis, held in London in 1901, Professor Koch delivered an address, in which he stated that bovine tuberculosis and human tuberculosis are not one and the same disease, and that the risk of infection from cattle to human beings is so small that it is not advisable to enforce burdensome restrictions for the sake of preventing such infection. He supported this opinion partly by the negative results of some inoculation - experiments on animals, partly by hospital statistics, as to the rarity of primary tuberculous infection of the intestines. In the subsequent criticism of this address, Lord Lister, Professor McFadyean, Professor Nocard of Paris, Professor Thomassen of Utrecht, and Dr Ravenel of Philadelphia, were all opposed to him: and, in the general judgment of men well qualified to study the matter, he failed to prove his point. An admirable account of his address, and of the discussion which followed it, is given by Professor Stengel and Dr Edsall of Philadelphia, in Gould's *Year-Book*, 1902. The chief results of the Congress are described by Dr Priestley, Medical Officer of Health for Lambeth, in the *Medical Annual*, 1902. He says:—

"The year 1901 will long be remembered as the year in which the British Congress on Tuberculosis was held in London. Three important addresses were delivered, and many interesting papers read and discussed. The feature of the Congress was Professor Koch's address on 'The combating of tuberculosis, in the light of the experi-

ence that has been gained in the successful combating of other infectious diseases.' Professor Koch made the startling statement that bovine and human tuberculosis are different diseases, and, practically, not intercommunicable. In other words, that the bacillus of bovine tuberculosis is not the same as that of the human disease, and that the bacilli from the latter will not infect cattle. By those who have had any experience in the subject, it will be admitted that there is a good deal to be said on the other side, and the very few experiments (twenty-five) mentioned by Professor Koch are certainly not sufficient to settle the point. Even assuming that Professor Koch's few experiments proved his case, viz., that experimentally it is impossible to graft the human disease on to cattle, the converse does not by any means follow, viz., that the bovine disease cannot be grafted on to man. The literature of the disease appears to point to the opposite conclusion. In any case, the subject is one that calls urgently for a Governmental inquiry, and it is satisfactory to be able to report that a Royal Commission, consisting of Sir M. Foster, Professor G. Sims Woodhead, Dr Sidney Martin, Professor McFadyean, and Professor Boyce, has been appointed. The German Government, too, has appointed a Commission, whilst experiments are being conducted in certain of the American States, and the Council of the Royal Agricultural Society has made a grant for special research—all dealing with the same subject.

"The point at issue is a most vital one, and must be settled once and for all; otherwise the statement as made by Professor Koch, to the effect that in his opinion stringent measures need no longer be taken with regard to meat inspection and

milk pasteurisation or sterilisation, is calculated to do much harm and to render sanitary authorities and their officers somewhat lax in connection with the protecting of meat and milk supplies from contamination with the bacillus tuberculosis. In the past, much energy and money have been expended in this direction, and much hardship imposed upon dairymen, butchers, and others. The general feeling of the Congress was that, whether the Koch theory were true or not, it was undesirable that meat or milk, when asked for, should be offered accompanied with bacilli of tuberculosis or any other disease—a statement with which all people must agree. Tubercle-infected milk is certainly not of the 'nature, quality, and substance demanded,' and so may come to be dealt with under the Food and Drugs (Adulteration) Acts.

"As it was felt that this outcome of the address was unavoidable, and that local authorities might be lax in dealing with tuberculous meat and milk, the Local Government Board was approached, with the result that a letter was issued by the Board on 6th September to the various local authorities in England and Wales, impressing upon them that, pending the investigations and report of the Royal Commission, there should be no relaxation on their part, or on the part of their officers, in the taking of proper measures for dealing with tuberculous meat and milk intended for the use of man. . . .

"With regard to the notification of phthisis, all agreed that a voluntary or optional system, such as that in operation at Brighton, Manchester, etc., was much to be desired, and would undoubtedly assist in enabling authorities to teach the people the danger of the disease, and the importance of simple

preventive measures being taken. . . . All cases of tuberculosis need not be notified, nor even all cases of consumption, but only those that are sources of danger owing to domestic conditions. Such a limited notification must be optional."

IV

DIPHTHERIA

THE bacillus of diphtheria, the Klebs-Loeffler bacillus, was first described by Klebs in 1875, and was first obtained in pure culture by Loeffler in 1884. Its isolation was a matter of great difficulty, and the work of many years, because of its association in the mouth with other species of bacteria. The following table, from Hewlett's *Manual of Bacteriology*, is a good instance of one of many practical difficulties. Out of 353 cases of diphtheria, bacteriological examination found the diphtheria-bacillus alone in 216 cases. In the remaining 137 it was associated with the following organisms :—

Streptococci	6
Staphylococci	55
Bacilli	19
Torulæ	9
Sarcinæ	6
Streptococci and micrococci	2
Micrococci and bacilli	9
Streptococci and bacilli	1
Torulæ and bacilli	1
Micrococci and sarcinæ	6
Micrococci and torulæ	4
Many forms present together	19
	137

In December 1890 came the news that Behring and Kitasato had at last cleared the way for the use of an antitoxin :—

"Our researches on diphtheria and on tetanus have led us to the question of immunity and cure of these two diseases; and we succeeded in curing infected animals, and in immunising healthy animals, so that they have become incapable of contracting diphtheria or tetanus."

Aronsen, Sidney Martin, Escherich, Klemensiewicz, and many more, were working on the same lines; and in 1893, Behring and Kossel and Heubner published the first cases treated with antitoxin. Then, in 1894, came the Congress of Hygiene and Demography at Budapest, and Roux's triumphant account of the good results already obtained. Thus the treatment is not ten years old; but, if the whole world could tabulate its results, the total number of lives saved would already be somewhere about a quarter of a million. Men found it hard at first to believe the full wonder of the discovery: the medical journals of 1895 and 1896 still contain the fossils of criticism—all the *may be* and *must be* of the earlier debates on the new treatment. The finest of all these fossils is embedded in the *Saturday Review* of 2nd Feb. 1895—*It is a pity that the English press should continue to be made the cat's-paw of a gang of foreign medical adventurers.* To get at the truth, we must reckon in thousands: take, out of a whole mass of evidence, all just alike, the reports from London, Berlin, Munich, Vienna,

Strasbourg, Cairo, Boston, and New York; these to begin with. Or the following facts, cut almost at random out of the medical journals:—

"The medical report of the French army states that since the introduction of the serum-treatment of diphtheria, the mortality among cases of that disease had fallen from 11 per cent. to 6 per cent." (*Brit. Med. Journ.*, 3rd September 1898.)

"Professor Krönlein (Zürich) exhibited statistical tables, showing that the prevalence of diphtheria in the canton of Zürich had been nearly uniform during the past fifteen years; and that the mortality rapidly decreased as soon as antitoxic serum was used on a somewhat larger scale. In his clinic, all the patients were examined bacteriologically, and serum was administered in every case of diphtheria without exception. Of 1336 cases treated before the serum-period, 554 = 39.4 per cent. died; whilst during the serum-period there were 55 deaths among 437 cases = 12 per cent. In cases of tracheotomy, the death-rates before and during the serum-period were 66 and 38.8 per cent. respectively." (*Lancet*, 7th May 1898, Report of German Surgical Congress at Berlin.)

"Dr Kármán was entrusted by the Hungarian Government with the task of instituting measures for preventing the spread of diphtheria in a village and its neighbourhood. As general hygienic regulations accomplished nothing, he tried preventive inoculation. . . . Among 114 children thus treated, there was during the next two months no case of diphtheria, although the disease was prevalent in the village up to the date at which inoculation commenced, and continued to rage in the surrounding villages afterwards. During those two months,

only one case of diphtheria appeared in the village, and that was in an uninoculated child; while, in the previous five months, 18.3 per cent. of the village children had been attacked, of whom eight died, six not having been treated with serum. Considering the wretched hygienic condition of the village, the harmlessness of preventive inoculations, and the continuance of the disease in the neighbouring villages, where diphtheria-vaccination was not carried out, the extraordinary value of the inoculations, in the prophylaxis of diphtheria, can hardly be denied." (*Brit. Med. Journ.*, 16th January 1897.)

"The most striking confirmation of the value of antitoxin has been afforded where the supply ran short during an epidemic. In Baginsky's clinic, the interruption of the serum-treatment promptly raised the mortality from 15.6 to 48.4 per cent." (*Brit. Med. Journ.*, 20th October 1895.)

"In an analysis of the ratio of mortality in 266 German cities of about 15,000 inhabitants, it was found that the ratio of mortality per 100,000 of the living, before antitoxin was used, varied from 130 to 84 from 1886 to 1893, while the ratio from 1894 to 1897 varied from 101 to 35. It is a significant fact that during 1894, when, although antitoxin was used to a certain extent, it was not in general use, the ratio was 101; that when antitoxin was used more extensively, in 1895, the ratio was 53; that in 1896 it was 43; that in 1897, when antitoxin was very generally used, the rate fell to 35." (*Trans. Massachusetts Med. Soc.*, 1898.)

"Dr Gabritchefski points out that in recent years the number of persons (in Russia) attacked by the disease has increased, the figures for the whole of Russia rising from about 100,000 or 120,000, ten years ago, to considerably over

200,000 in 1897. The introduction of the serum treatment has, however, had a marked effect on the mortality of the disease; and the actual number of deaths from diphtheria has either not increased at all, or has slightly diminished." (*Lancet*, 5th Aug. 1899.)

Of course there will still be bad diphtheria years and good diphtheria years: for example, the death-rate of the population of England, from diphtheria, was higher during the years 1893-1899 than during the years 1889-1892. The following table, from Gould's *Year-Book* for 1902, p. 647, gives the death-rates from diphtheria and "croup" in different countries for the years 1889-1898. The figures are expressed as a death-rate per 10,000 of the living population:—

Year.	Germany.	Austria.	Belgium.	France.	Holland.	Switzerland.	England.
1889 .	10.9	7.1	3.9	6.6	...	6.0	2.6
1890 .	10.1	7.3	3.7	6.1	...	7.6	2.4
1891 .	8.5	8.8	3.3	6.0	4.9	8.2	2.1
1892 .	9.7	9.5	2.6	5.4	4.5	5.2	2.5
1893 .	12.6	9.6	4.0	5.5	4.0	10.2	4.3
1894 .	10.2	10.2	4.6	4.1	3.3	8.0	3.8
1895 .	5.4	6.3	2.9	1.9	1.4	3.4	3.5
1896 .	4.3	4.9	1.6	1.8	2.5	3.4	3.9
1897 .	3.5	4.7	1.3	1.2	2.2	3.0	3.1
1898 .	3.4	3.8	1.4	1.2	1.7	3.7	3.1

Antitoxin can no more prevent a bad diphtheria year than an umbrella can prevent a wet day. But in outbreaks of diphtheria such as occur in a village, an asylum, a school, or a large family of young children, it can be used, and is used, as a prophylactic, and with admirable results. The example

of Dr Kármán, just quoted, is one of the earliest instances of this preventive use of antitoxin: other instances, of equal importance, are given in the *Boston Medical and Surgical Journal*, December 1897, and March 1898; and in the *Lancet*, 2nd April 1898, and 28th January 1899. A summary of more recent experiences of this preventive use of antitoxin in different countries is given by Dr Wilcox of New York, and Dr Stevens of Philadelphia, in Gould's *Year-Book* for 1902:—

"At a meeting of the Société de Pédiatrie (Paris), held June 1901, a resolution was adopted affirming that preventive inoculations present no serious dangers, and confer immunity in the great majority of cases for some weeks, and recommending their employment in children's institutions and in families in which scientific surveillance cannot be exercised. Netter stated that he had collected 32,484 observations (cases) of prophylactic injections, and after eliminating cases in which the disease developed in less than twenty-four hours after injection, or more than thirty days after, there were 6 per cent. of failures. On the other hand, the author stated that he had recently made ninety preventive injections with but 2.17 per cent. of failures. Potter reports a series of twenty-four families in which preventive injections were used. Only one case of diphtheria occurred. In another series of cases, in which no prophylactic injections were given, the disease occurred secondarily in one-third of the houses, and one-sixth of the inmates contracted the disease, in spite of the fact that a large number of the primary cases were removed to the hospital. Blake reports a series of thirty-

five prophylactic injections. The treatment was instituted after three cases of diphtheria had developed in a children's home. No secondary cases developed. Voisin and Guinon describe an epidemic of diphtheria in the Salpetrière Hospital among idiots and epileptics. Prophylactic injections were given to all those exposed to the contagion. After that, but four cases appeared, all mild in character. One severe case developed, however, two weeks later, ending fatally in twenty-four hours, showing that the prophylactic action of the antitoxin, while efficacious, is not of very long duration."

It would be easy to prolong *ad infinitum* the proofs of the curative and preventive efficacy of the antitoxin: it would be impossible to find any evidence to be weighed for one moment against these proofs. Finally, there are four records that ought to be quoted more fully: the 1894 report from the Hospital for Sick Children, Paris; the 1896 report of the American Pædiatric Society; the 1898 report of the Clinical Society of London; and the records of the Hospitals of the London Metropolitan Asylums Board.

I

The report from the Hospital for Sick Children, Paris, is contained in a memoir, *Sérum-Thérapie de la Diphtérie*, the joint work of MM. Roux, Martin, and Chaillon (*Annales de l'Institut Pasteur*, September 1894). It gives the results of the serum-treatment during February to July 1894.

The cases were not selected: the antitoxin was given in every case that was proved, by bacteriological examination, to be diphtheria—with the exception of 20 cases where the children were just dying when they were brought to the hospital. No change was made either in the general treatment or in the local applications to the throat; these were the same that had been used in former years: *le sérum est le seul élément nouveau introduit.*

In 1890-1893, before the serum-treatment, 3971 children were admitted to the diphtheria wards, and 2029 of them died. The percentage of these deaths was—

In 1890	55.88	Average = 51.71.
„ 1891	52.45	
„ 1892	47.64	
„ 1893	48.47	

The serum was used from 1st February to 24th July 1894. During this period 448 children were admitted, of whom 109 died = 24.5.

During the same period (February to June) the Trousseau Hospital, where the serum was not used, had 520 cases, with 316 deaths = 60.0.

The cases at the Hospital for Sick Children must be divided into those that required tracheotomy and those that did not require it:—

MORTALITY AMONG CASES NOT REQUIRING TRACHEOTOMY.

In 1890	47.30	Average = 33.94.
„ 1891	46.64	
„ 1892	38.8	
„ 1893	32.02	

During the serum-period, the mortality of these cases was 12.0. At the Trousseau Hospital, without the serum, the mortality of these cases during the same period was 32.0.

MORTALITY AMONG CASES REQUIRING TRACHEOTOMY.

In 1890	76.35	Average = 73.49.
„ 1891	68.36	
„ 1892	74.6	
„ 1893	73.45	

During the serum-period, the mortality of these cases was 49.0. At the Trousseau Hospital, without the serum, the mortality of these cases during the same period was 86.0.

Setting aside, out of the 448 children, those cases of "membranous sore throat" or "pseudo-diphtheria," in which the Klebs-Loeffler bacillus was not found, there remain 320 cases where it was found. Of these 320 children, 20 were just dying on admission, and did not receive the serum. Of the 300 who received it, 78 died = 26.0. Before the serum-period, the mortality of these cases at the same hospital was about 50.0. The complications of diphtheria, such as paralysis, were much less frequent during the serum-period than they had been before it.

II

Report of the American Pædiatric Society's Collective Investigation into the use of Antitoxin in the treatment of diphtheria in private practice. (Eighth Annual Meeting, Montreal, May 1896.)

From the *New York Medical Record*, 4th July 1896.

This vast collection of cases is of special interest, because they occurred in private practice. In most of them the nature of the disease was proved by bacteriological examination; in the rest, the clinical evidence was decisive: "It is possible that among the latter we have admitted some streptococcus cases, but the number of such is certainly very small." All other doubtful cases, 244 in number, were excluded.

Three thousand three hundred and eighty-four cases were reported by 613 physicians from 114 cities and towns, in 15 different States, the District of Columbia, and the Dominion of Canada. To these 3384 cases were added 942 cases from tenement-houses in New York, and 1468 cases from tenement-houses in Chicago. The New York and Chicago cases were, most of them, treated by a corps of inspectors of the Health Board of the city; and the municipal surveillance was very strict at Chicago:—

"There are very few hospitals in America that receive diphtheria patients. . . . It was the custom in Chicago to send an inspector to every tenement-house case reported, and to administer the serum unless it was refused by the parents. These cases were therefore treated much earlier, and the results were correspondingly better than were obtained in New York, although the serum used was the same in both cities, viz., that of the New York Health Board."

The sum total of results was 5794 cases, with

713 deaths = 12.3 per cent., including every case returned; but 218 were moribund at the time of injection, or died within twenty-four hours of the first injection. "Should these be excluded, there would remain 5576 cases in which the serum may be said to have had a chance, with a mortality of 8.8 per cent."

Of	996	cases injected	on the first day of the disease,	49 died =	4.9 %
„	1616	„	on the second „	120 „ =	7.4 „
„	1508	„	on the third „	134 „ =	8.8 „
„	758	„	on the fourth „	147 „ =	20.7 „
„	690	„	on or after the fifth „	244 „ =	35.3 „

And in 232 cases, where the day of injection was unknown, there were 19 deaths = 8.2 per cent.

"No one feature of the cases of diphtheria treated by antitoxin has excited more surprise among the physicians who have reported them than the prompt arrest, by the timely administration of the serum, of membrane which was rapidly spreading downward below the larnyx. Such expressions abound in the reports as 'wonderful,' 'marvellous,' 'in all my experience with diphtheria, have never seen anything like it before,' etc.

"Turning now to the operative cases, we find the same remarkable effects of the antitoxin noticeable. Operations were done in 565 cases, or in 16.7 per cent. of the entire number reported. Intubation was performed 533 times, with 138 deaths, or a mortality of 25.9 per cent. In the above are included 9 cases in which a secondary tracheotomy was done, with 7 deaths. In 32, tracheotomy only was done, with 12 deaths, a

mortality of 37.4 per cent. Of the 565 operative cases, 66 were either moribund at the time of operation or died within twenty-four hours after injection. Should these be deducted, there remain 499 cases operated upon, by intubation or tracheotomy, with 84 deaths, a mortality of 16.9 per cent.

"Let us compare the results of intubation, in cases in which the serum was used, with those obtained with this operation before the serum was introduced. Of 5546 intubation cases in the practice of 242 physicians, collected by M'Naughton and Maddren (1892), the mortality was 69.5 per cent. Since that time, statistics have improved materially by the general use (in and about New York, at least) of calomel fumigations. With this addition, the best results published (those of Brown) showed in 279 cases a mortality of 51.6 per cent.

"But even these figures do not adequately express the benefit of antitoxin in laryngeal cases. Witness the fact that over one-half the laryngeal cases did not require operation at all. Formerly, 10 per cent. of recoveries was the record for laryngeal cases not operated upon. Surely, if it does nothing else, the serum saves at least double the number of cases of laryngeal diphtheria that has been saved by any other method of treatment."

III

In 1898, the Clinical Society published the Report of their Special Committee, based on 633 cases (*Trans. Clin. Soc.*, xxxi., 1898, pp. 1-50). The

whole report should be read carefully; but there is room here for nothing more than the latter part of it. This is given at length.

A

Table showing the General Mortality of cases treated, on the same day of the disease, with and without Antitoxin.

Antitoxin Committee: 633 Cases treated with Antitoxin.				Metropolitan Asylums Board, 1894: 3042 Cases treated without Antitoxin.				Difference of percentage.
Day of the Disease on which Treatment was begun.	Cases.	Deaths.	Mortality per cent.	Day of Admission to Hospital.	Cases.	Deaths.	Mortality per cent.	
1st	20	2	10.0	1st	133	30	22.5	12.5
2nd	92	10	10.8	2nd	539	146	27.0	16.2
3rd	133	20	15.0	3rd	652	192	29.4	14.4
4th	130	26	20.0	4th	566	179	31.6	11.6
5th and after.	258	66	25.5	5th	1152	355	30.8	5.3
Totals .	633	124	19.5	Totals	3042	902	29.6	10.1

B

Summary and Conclusions of the Committee's Report.

"The material for the investigation of the clinical value of the antitoxin serum in the treatment of diphtheria was not obtained from selected, but from consecutive, cases, reported from the general hospitals and the fever hospitals of the Metropolitan Asylums Board; all were made use of which fulfilled the requirements of the Committee.

"The Committee rejected all cases in which

satisfactory proof of the existence of true diphtheria was not shown, either by the presence of the *Bacillus diphtheriæ* upon bacteriological examination, or by the occurrence of paralysis in the course of the illness. All were also rejected in which the amount of antitoxin administered was stated in cubic centimetres and not in normal units, the Committee having no means by which the strength of the antitoxin could in these cases be determined.

"Six hundred and thirty-three cases form the basis on which the report is drawn up; 549 were treated with antitoxin obtained from the laboratory of the Royal Colleges of Physicians and Surgeons; the remainder, 84 in number, were injected with antitoxin obtained from other sources. In nine instances, antitoxin from two different sources was injected into the same patient.

"Statistics of the disease before the use of antitoxin are introduced as control series; these were obtained from the fever hospitals of the Metropolitan Asylums Board, and from the general hospitals; and, like the antitoxin series, are compiled from consecutive and not from selected cases.

"The general mortality, under the antitoxin treatment, was 19.5 per cent.; a reduction of 10 on the percentage mortality of the cases treated in the hospitals of the Metropolitan Asylums Board in 1894. If 15 fatal cases, in which death took place within twenty-four hours of the first injection, be deducted, the mortality falls to 15.6 per cent.; which is very little more than half the mortality during 1894 under other forms of treatment.

"The lessened mortality is especially noticeable in the earlier years of life, the percentage mortality of children under five being 26.3, as opposed to 47.4. In the next period of five years, the percentage of mortality is 16.0, as opposed to 26.0; whilst after ten years of age the difference in the mortality is slight.*

"Laryngeal diphtheria is admittedly the most dangerous form. The laryngeal cases have a percentage mortality of 23.6 in the antitoxin, as compared with 66.0 in the non-antitoxin series. In the cases in which laryngeal symptoms are so severe as to necessitate tracheotomy, the saving of life by the use of antitoxin is very marked, the mortality being reduced one-half, to 36.0 as opposed to 71.6 per cent.

"The strongest evidence of the value of the antitoxin treatment is that, in addition to reducing the general mortality by one-third, the duration of life in the fatal cases is decidedly prolonged. These two facts taken together conclusively prove the beneficial effects of the antitoxin treatment.

"The incidence of paralysis is greater in the antitoxin than in the control series. This increased number is partly explained by the lessened mortality, and partly by the longer duration of life in the fatal cases affording time for the development of paralytic symptoms. The percentage mortality of those who had some form or other of paralysis is lower in the antitoxin than in the control series; so that, notwithstanding the apparent greater risk of paralysis

* After childhood, the disease is much less fatal.

supervening, the probability of final recovery is greater.

"No definite conclusion can be drawn, for the reasons stated in the body of the report, as to the advantage of administering the whole of the antitoxin within forty-eight hours of the first injection, or continuing it for a longer period; but evidence is afforded of the importance of its administration as early as possible in the course of the disease; the percentage mortality in cases injected on the first and second days of the disease being 10.7, as compared with 25.5 for those first receiving the injection on the fifth or some subsequent day.

"No conclusion can be drawn, from the cases reported on, as to the amount of antitoxin which should be used to produce the best effects; but they show that the administration of very large doses is followed by no pronounced ill effects.

"The injection of antitoxin is responsible for the production of rashes, joint-pains, and possibly for the occurrence of late pyrexia.* In 34.7 per cent. the injections were followed by rashes. Some amount of fever accompanied the rash in 60 per cent. In only 9.4 per cent. of those in whom rashes were observed did death ensue.

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* Since the date of this report, much has been done to obviate these faults of the serum-treatment. Take, for instance, M. Spronck's paper in the *Annales de l'Institut Pasteur*, October 1898: "Influence favourable du chauffage du sérum antidiphtérique sur les accidents post-thérapiques;" or the earlier paper, on the same subject, by MM. Béclère, Chambon, and Ménard.

"Joint-pains were observed in 40, or 6.3 per cent. of the whole number, and all but five of them had a rash as well.

"In 26, or 65 per cent. of the joint-pains, some rise of temperature accompanied the pain. A rise of temperature during convalescence, accompanied by either rash or joint-pain, occurred in 27, or 4.2 per cent. of the whole number.

"No connection could be traced between the amount of antitoxin administered and the occurrence of rashes or late pyrexia, but the pain in and about the joints appears to have a relationship to the amount of antitoxin used.

"The results of the Committee's investigation tend to show that by the use of antitoxin—

1. The general mortality is reduced by one-third.
2. The mortality in tracheotomy falls by one-half.
3. Extension of membrane to the larynx very rarely occurs after the administration of antitoxin.
4. The duration of life in the fatal cases is decidedly prolonged.
5. The number of fatal cases is less when antitoxin is used early in the illness than in those which do not receive it until a later period.
6. The frequency of the occurrence of paralysis is not diminished, but the percentage of recoveries in cases with paralysis is slightly increased.*

* For an exhaustive and final study of the diphtheritic paralyses, see Dr Woollacott's essay in the *Lancet*, 26th August 1899: "The use of antitoxic serum in the treatment of diphtheria has, up to the present time, in the London fever hospitals, had two main results—the death-rate has fallen,

7. Rashes are produced in about one-third of the cases, and are attributable to the antitoxin.

8. Pain, and occasionally swelling about the joints, are produced in a number of cases.

9. Even when used in large doses, no serious ill effects have followed the injection of antitoxin."

IV

The use of the antitoxin in the hospitals of the Metropolitan Asylums Board began in 1895. It had been used in 1894 on a few cases only; and during that year it had been procured with much difficulty from various sources, chiefly from the Institute of Preventive Medicine. On 9th November 1894, the Board applied to the Laboratories' Committee of the Royal Colleges of Physicians and of Surgeons, asking them to undertake the supply. Arrangements were made for this purpose;

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while the paralysis-rate has risen. In the hospitals of the Metropolitan Asylums Board, the former has been reduced from 29 per cent. to 15.3 per cent., while the latter has risen from 13 per cent. to as high as 21 per cent. in 1896. This increase of paralysis is chiefly due to the fact that many more patients now recover from the primary disease, and live long enough for paralysis to show itself. *During the last two years, however, the occurrence of paralysis has began to diminish in frequency. . . . The earlier antitoxin is given in diphtheria, the less likely is paralysis to follow.*" It is to be borne in mind that post-diphtheritic paralysis, in the great majority of cases, affects only a very small group of muscles; of Dr Woollacott's tabulated cases, 377 were of this kind, and 97 were severe. And "the type of paralysis has, on the whole, become less severe, or at all events less dangerous to life."

and the sum of £1000 was given by the Goldsmiths' Company. The letter offering this gift is pleasant reading now :—

"The attention of the Goldsmiths' Company has been drawn to the reports of the antitoxin treatment of diphtheria, which has recently created so much interest, both on the Continent and in this country: and the Company are led to believe that, although this treatment has not, perhaps, as yet passed out of the stage for experiment, there is much reason to hope that further investigations may lead to the attainment of a remedy which will largely reduce the mortality arising from this terrible disease.

"The Company are informed that there is great difficulty at the present time in obtaining a supply of serum adequate to the treatment of patients on an extended scale, and that the cost of the serum is also heavy. The Company also understand that while, on the Continent, experiments are being continued with funds provided from public sources, the work must be left in this country to private enterprise and liberality. Under these circumstances the Company have decided to make a grant of £1000 for the purpose of prosecuting research work in connection with this treatment, with which they desire to combine, if possible, the supply of serum for use among the poorer classes of the community."

Dr Sims Woodhead, then Director of the Laboratories of the Conjoint Colleges, now Professor of Pathology at Cambridge, was put in charge of the bacteriological work and the pre-

paration of the serum, with a host of expert colleagues: the adminstration of the treatment was the work of the medical officers of the hospitals of the Metropolitan Asylums Board. The serum was used for a few weeks only in 1894; the cases thus treated were excluded from the statistical tables for that year. Thus, 1894 was the last non-antitoxin year, and 1895 was the first antitoxin year.

The percentage of mortality from diphtheria in all the Board hospitals together is as follows. The disease was first admitted in 1888: this year is therefore reckoned as incomplete:—

1888 (incomplete year)	59.35	1895 (first antitoxin year)	22.55
1889	40.74	1896	20.80
1890	33.55	1897	17.50
1891	30.63	1898	15.50
1892	29.35	1899	14.05
1893	30.42	1900	12.01
1894	29.64		

The experiences of 1895 are given in the following passages from the joint report to the Board from the medical superintendents:—

"The period covered by the report extends from 1st January 1895 to 31st December of the same year. During this time—with the exception of an interval of three months at the Eastern Hospital, when its use was suspended; of three months at the Fountain, and to a considerable extent throughout the year at the South-Eastern Hospital, when all cases were consecutively treated, irrespective of their severity—the serum was administered *only to cases which at the time of admission were severe, or which threatened to become so.* In a certain number,

the patients being moribund at the time of their arrival, and beyond the reach of any treatment, no antitoxin was given. *No change has taken place during the year in the local treatment of the cases, nor has there been any new factor in the treatment other than the injection of antitoxin.*

"It must be clearly understood that, with the exceptions previously stated, it has been the practice at each of the hospitals to administer serum to *those cases only in which the symptoms on admission were sufficiently pronounced to give rise to anxiety, the mild cases not receiving any.*

"*No less than* 46.4 *per cent. of the antitoxin cases were under five years of age, against* 32.5 *per cent. in the non-antitoxin group;* and only 16.1 per cent. in the former class were over ten years of age, against 33.8 per cent. in the latter. The high fatality of diphtheria in the earlier years of life is notorious.

"It is obvious, therefore, that to compare the mortality of those treated with antitoxin with that of those which during the same period were not so treated, would be to institute a comparison between the severe cases and those of which a large proportion were mild. This would clearly be misleading.

"The only method by which an accurate estimate can be obtained as to the merits of any particular form of treatment, is by comparing a series of cases in which the remedy has been employed with another series not so treated, but which are similar, so far as can be, in other respects. This, in the present instance, is impossible; but, having regard to the fact that 61.8 of the 1895 cases were treated with serum, an approximately accurate conclusion can be drawn by contrasting all cases of diphtheria

completed during 1895, the antitoxin period, with all cases completed during 1894.

"The year 1894 has been selected for the purpose of comparison, not only because it is the year immediately preceding the antitoxin period, but because the average severity of the cases has been, in our opinion, about equal. Moreover, the death-rate in 1894 was slightly lower than it had been in any previous year.

". . . Of 3042 patients of all ages treated during 1894, 902 died—a mortality of 29.6 per cent.; whereas, of 3529 cases treated during 1895, 796 died—a mortality of 22.6 per cent.; the difference in percentage between the two rates being therefore 7.1. This, assuming that the former rate would otherwise have been maintained, represents a saving of 250 lives during the past year.

INFLUENCE OF AGE.

Table showing variations in reduction of mortality obtained with Antitoxin at different ages.

Ages.	Antitoxin Cases, 1895.			All Cases, 1895.			All Cases, 1894.			Diff. in Mortalities, 1894 and 1895.
	Cases.	Deaths.	Mortality per cent.	Cases.	Deaths.	Mortality per cent.	Cases.	Deaths.	Mortality per cent.	
Under 5 .	1013	379	37.4	1453	497	34.2	1171	556	47.4	13.2
„ 10.	1829	575	31.4	2720	744	27.3	2246	836	37.2	9.9
„ 15.	2056	606	29.4	3144	779	24.7	2609	877	33.6	8.9
All ages .	2182	615	28.1	3529	796	22.5	3042	902	29.6	7.1

For every age-group, with the single exception of that comprising the years 15 to 20 (the numbers of which are small), the percentage mortality was less in the 1895 than in the 1894 cases. The reduction in mortality was greatest in early life.

INFLUENCE OF TIME OF COMING UNDER TREATMENT.

Table showing percentage mortality in relation to day of disease on which cases came under treatment.

Day of Disease.	1894.	1895.	Difference.
1st . .	22.5	11.7	10.8
2nd . .	27.0	12.5	14.5
3rd . .	29.4	22.0	7.4
4th . .	31.6	25.1	6.5
5th and over .	30.8	27.1	3.7
Total .	29.6	22.5	7.1

"It will be seen that the percentage mortality of cases admitted on the same day of disease is less in every instance in the year 1895. The difference is most marked in the case of those patients who were admitted on the first and second day of illness, viz., 10.8 and 14.5 respectively.

"Both in 1894 and 1895, no less than over 37 per cent. of the patients were admitted on, or after, the fifth day of disease. And, moreover, while in 1894 as many as 59.2 per cent. of the fatal cases were not brought under treatment until the fourth day, or later, in 1895, the antitoxin year, the proportion was even higher, viz., 67.7 per cent.

Laryngeal Cases.

"The tracheotomy results at each hospital are more favourable in the year 1895 than in 1894, the mortality ranging in the latter year at the different nospitals between 90 per cent. and 59.4 per cent., whereas in 1895 the range was from 56.2 to 40.5.

"The combined tracheotomy mortality for all

the hospitals, which in 1894 was 70.4 per cent., has fallen to 49.4 per cent. in 1895. This is a lower death-rate than has ever been recorded in any single hospital of the Board for a year's consecutive tracheotomies. In other words, rather more than 50 per cent. of children on whom the operation has been performed have been saved since the employment of antitoxin. In one of the hospitals no less than a fraction under 60 per cent. survived, although the recoveries in that hospital in any previous year did not exceed 25 per cent., and in the preceding year—viz., 1894—were as low as 10 per cent.

"The improved results in the tracheotomy cases of 1895 have also been shared by analogous cases in which the operation was not performed. The percentage mortality of all laryngeal cases has fallen from 62 in 1894 to 42.3 in 1895.

"Moreover, the number of laryngeal cases which required tracheotomy has fallen in 1895 to 45.3 per cent., whereas in 1894 it was 56 per cent.

"The following tables briefly summarise the foregoing results. As no returns for 1894 were furnished by the Fountain Hospital by reason of the smallness of the numbers, the Fountain cases have also been omitted from the 1895 figures, in order that the two series may be rendered strictly comparable:—

1. *Comparative Mortality of Laryngeal Cases at all Hospitals, except the Fountain.*

Year.	Cases.	Deaths.	Percentage Mortality.
1894	466	289	62.0
1895	468	196	41.8

2. *Comparative Results in Tracheotomy Cases at all Hospitals, except the Fountain.*

Year.	Cases.	Deaths.	Percentage Mortality.
1894	261	184	70.4
1895	219	108	49.3

3. *Comparative Number of Laryngeal Cases which required Tracheotomy at all Hospitals, except the Fountain.*

Year.	Cases.	Tracheotomies.	Percentage of Tracheotomies.
1894	466	261	56.0
1895	468	219	46.8

"On these tables further comment seems unnecessary.

Summary.

"The improved results in the diphtheria cases treated during the year 1895, which are indicated by the foregoing statistics and clinical observations, are—

1. A great reduction in the mortality of cases brought under treatment on the first and second day of illness.

2. The lowering of the combined general mortality to a point below that of any former year.

3. The still more remarkable reduction in the mortality of the laryngeal cases.

4. The uniform improvement in the results of tracheotomy at each separate hospital.

5. The beneficial effect produced on the clinical course of the disease.

Conclusions.

"A consideration of the foregoing statistical tables and clinical observations, covering a period of twelve months, and embracing a large number of cases, in our opinion sufficiently demonstrates the value of antitoxin in the treatment of diphtheria.

"It must be clearly understood, however, that to obtain the largest measure of success with antitoxin it is essential that the patient be brought under its influence at a comparatively early date—if possible, not later than the second day of disease. From this time onwards, the chance of a successful issue will diminish in proportion to the length of time which has elapsed before the treatment is commenced. This, though doubtless true of other methods, is of still greater moment in the case of treatment by antitoxin.

"Certain secondary effects not unfrequently arise as a direct result of the injection of antitoxin in the form in which it has at present to be administered, and even assuming that the incidence of the normal complications of diphtheria is greater than can be accounted for by the increased number of recoveries, we have no hesitation in expressing the opinion that these drawbacks are insignificant when taken in conjunction with the lessened fatality which has been associated with the use of this remedy.

"We are further of the opinion that in antitoxic serum we possess a remedy of distinctly greater value in the treatment of diphtheria than any other with which we are acquainted."

It is unnecessary to quote fully the reports for 1896 and 1897. The mortality per cent. of the cases stands as follows :—

	All Cases.	Laryngeal Cases.	Tracheotomies.
1894	29.6	62	70.4
1895	22.5	42.3	49.4
1896	20.8	29.6	41.0
1897	17.5	30.9	40.5

In the reports for 1898 and subsequent years, a change was made: *All deaths from intercurrent diseases, such as measles, etc., were included.* The 1898 report is as follows :—

"The following three tables show the result of the antitoxin treatment in diphtheria cases. Each table is divided into two halves, one showing only cases treated with antitoxin, the other all cases however treated.

"Owing to the fact that severe cases are chiefly selected for the antitoxin treatment, the mild cases not being so treated, the second set of figures is probably a better guide than the first as to the success of the treatment, as has been urged in the fuller reports on this subject published in the annual volumes for 1895 and 1896.

"In the following tables, all deaths from intercurrent diseases, such as measles, etc., have been included. In the reports just alluded to, all cases complicated by intercurrent disease were excluded. As the death-rate amongst such cases is heavy, the case-mortalities for 1898 are all somewhat higher than if the figures had been compiled on the plan

adopted in 1895 and 1896. In 1897 some of the hospitals have included such complicated cases, others not.

1898.

1. *All forms of Diphtheria.*

Cases treated with Antitoxin.			All Cases; both those treated with Antitoxin, and those not.		
Cases.	Deaths.	Mortality per cent.	Cases.	Deaths.	Mortality per cent.
5186	906	17.5	6372	990	15.5

2. *Laryngeal Cases.*

Cases treated with Antitoxin.			All Cases; both those treated with Antitoxin, and those not.		
Cases.	Deaths.	Mortality per cent.	Cases.	Deaths.	Mortality per cent.
624	199	31.9	654	225	34.4

3. *Tracheotomy Cases.*

Cases treated with Antitoxin.			All Cases; both those treated with Antitoxin, and those not.		
Cases.	Deaths.	Mortality per cent.	Cases.	Deaths.	Mortality per cent.
305	113	37.0	313	119	38.0

The tables for 1899 and 1900, like those for 1898, include all deaths from intercurrent diseases.

1899.

1. *All forms of Diphtheria.*

Cases treated with Antitoxin.			All Cases; both those treated with Antitoxin, and those not.		
Cases.	Deaths.	Mortality per cent.	Cases.	Deaths.	Mortality per cent.
7038	1082	15.38	8015	1126	14.05

2. *Laryngeal Cases.*

Cases treated with Antitoxin.			All Cases; both those treated with Antitoxin, and those not.		
Cases.	Deaths.	Mortality per cent.	Cases.	Deaths.	Mortality per cent.
669	190	28.4	687	201	29.3

3. *Tracheotomy Cases.*

Cases treated with Antitoxin.			All Cases; both those treated with Antitoxin, and those not.		
Cases.	Deaths.	Mortality per cent.	Cases.	Deaths.	Mortality per cent.
377	147	39.1	382	149	39.1

1900.

1. *All forms of Diphtheria.*

Cases treated with Antitoxin.			All Cases; both those treated with Antitoxin, and those not.		
Cases.	Deaths.	Mortality per cent.	Cases.	Deaths.	Mortality per cent.
7271	936	12.88	8225	987	12.01

2. *Laryngeal Cases.*

Cases treated with Antitoxin.			All Cases; both those treated with Antitoxin, and those not.		
Cases.	Deaths.	Mortality per cent.	Cases.	Deaths.	Mortality per cent.
777	182	23.20	799	196	24.57

3. *Tracheotomy Cases.*

Cases treated with Antitoxin.			All Cases; both those treated with Antitoxin, and those not.		
Cases.	Deaths.	Mortality per cent.	Cases.	Deaths.	Mortality per cent.
377	127	33.65	390	139	34.30

Any bad results that have been recorded from the use of the antitoxin are so rare, in comparison with the hundreds of thousands of injections made, that they do not come to be considered here. And, even though a few have occurred, we may be sure that some of them were due, not to the antitoxin, but to the natural course of the disease.* The lesser drawbacks, the occurrence of joint-pains and of rashes, are probably much less now than they were a few years ago, and will be further diminished.

It has been supposed, and said, that the use of the antitoxin increases the complications of the

* This, of course, does not apply to two instances, in 1901, of accidental contamination of serum. See, for an account of these, *The British Medical Journal*, November 1901.

disease. On this point, the best authority is Professor Woodhead's monumental Report (1901), dealing with the Metropolitan Asylums Board cases for 1895 and 1896. He sums up the matter thus :—

"The free use of antitoxin does not raise the percentage of cases of albuminuria. As regards vomiting, the statistics give little information, as vomiting is usually met with only in the very severe cases. This also holds good of anuria. The number of cases of adenitis appears to be distinctly reduced by the use of antitoxin, as the percentage of cases falls as the injections of antitoxin are pushed. The use of antitoxin has also had a perceptible effect in diminishing the cases of nephritis, and it certainly has not aggravated the kidney complications of diphtheria. There can be no doubt that in cases treated with antitoxin there is a greater percentage of cases in which joint-pains occur than in cases not so treated; these, however, are transitory, and are probably the result of some slight change in the blood set up by the action of the serum itself, and not by the antitoxic substance in the serum. The number of primary abscesses has undoubtedly been reduced by the use of antitoxin. It may also be accepted that antitoxic serum has some effect in temporarily raising the temperature, but only during the periods of joint-pains and serum rashes; all these, however, are of comparatively slight importance as compared with the effect the antitoxin has in diminishing the percentage mortality and alleviating the more severe symptoms.

"It is of importance to observe that amongst

the cases of paralysis following diphtheria the death-rate (32 per cent.) was actually higher amongst those not injected with antitoxin than amongst those where antitoxin was used (30.5 per cent.), although the former paralyses must be looked upon as being the result of a comparatively mild attack of the disease. From this it is evident that, when once paralysis supervenes in these cases, it is quite as fatal in its effects as in the cases (usually those of a more severe type) where antitoxin has been given. Antitoxin *cannot cure* the degeneration of the nerve, but it *can neutralise* the diphtheria toxin, and so put a stop to the advance of the degenerative changes due to its action. In 1896, when, of course, antitoxin was given much more freely, the percentage of deaths in the non-injected cases where paralysis had come on fell to 18.4.

"Antitoxin rashes occur at a comparatively late stage of the disease. They cannot be looked upon as in any way dangerous, although the secondary rise of temperature, and the irritation of the skin which usually accompany their presence are very undesirable complications, and may retard somewhat the convalescence of nervous and irritable patients.

"Antitoxin appears to diminish the liability of the lungs to inflammatory change in severe attacks of diphtheria."

Finally, there are Siegert's tables (1900), based on no less than 40,038 cases, during nine years, in sixty-nine hospitals, in Germany, Austria, Switzerland, and Paris, *Securus judicat orbis terrarum.* Siegert divides the nine years into a "pre-serum

period" (1890-93), an "introduction year" (1894), and a "serum period" (1895-98). The general mortality, in the pre-serum period, was 41.5, and in the serum period was 16.5. The mortality of operation cases was 60.0 in the pre-serum period, 53.7 in the introduction year, and 35.7 in the serum period. The proportion of operation cases to all cases, in twenty-one hospitals, was 47.2 in the pre-serum period, and 27.5 in the serum period.

Or, if it be better to finish this chapter with one recent opinion of the very highest authority, *The Medical Annual* for 1902 contains an article on diphtheria by Dr Goodall, Medical Superintendent of the Eastern Hospital of the Metropolitan Asylums Board. He says, "The writer has now, after a very large experience in the treatment of diphtheria, both without and with antitoxic serum, no hesitation in saying that the antitoxic treatment is *the* treatment." Or, for a final set of figures, there are Richardière's 1778 cases treated with antitoxin at the Trousseau Hospital, Paris. The gross mortality was 15.7 per cent. If those cases be excluded that were dying on admission and died within twenty-four hours after admission, the mortality was 11.5. And, of 1115 cases not requiring operation, the mortality was 5.5. In every one of the cases the diagnosis was confirmed by bacteriological examination.

V

TETANUS

BEFORE bacteriology, the cause of tetanus (lock-jaw) was unknown, and men were free to imagine that it was due to inflammation travelling up an injured nerve to the central nervous system. This false and mischievous theory was abolished by the experimental work of Sternberg (1880), Carle and Rattone (1884), and Nicolaier (1884), who proved, once and for all, that the disease is an infection by a specific flagellate organism. Their work was of the utmost difficulty, for many reasons. First, because tetanus, in some tropical countries, is so common that it may fairly be called endemic; and many of these tropical cases, there being no record of any external infection, had been taken as evidence that the disease can occur "of itself." Of this frequency of tetanus in tropical countries, Dr Patrick Manson, in his book on *Tropical Diseases* (1898), says:—

"Tetanus is an exceedingly common disease in some tropical countries. In Western Africa, for

example, a large proportion of wounds, no matter how trifling as wounds they may be, if they are fouled by earth or dirt, result in tetanus. The French in Senegambia have found this to their cost. A gentleman who had travelled much in Congoland told me that certain tribes poison their arrows by simply dipping the tips in a particular kind of mud. A wound from these arrows is nearly sure to cause tetanus. In many countries, so general and so extensive is the distribution of the tetanus bacillus that trismus neonatorum (tetanus of newly-born infants) is a principal cause of the excessive infant mortality."

Next, because the tetanus-bacillus has its natural abode in the superficial layers of the soil: here it is associated with a vast number of other organisms, so that its identification and isolation were a work of immeasurable complexity. What mixed company it keeps, is shown by Houston's estimate of the number of microbes per gramme in twenty-one samples of different soils. This number ranged from 8326 in virgin sand, and 475,282 in virgin peat, to 115,014,492 in the soil from the trench of a sewage-farm. In all rich and well-manured soil the tetanus-bacillus may possibly be present; but it was the work of years to dissociate it from the myriads of organisms outnumbering it.

Next, because it cannot be got to grow in cultures exposed to the air: its proper place is below the surface of the soil, away from the air; it is "strictly anaërobic," and the attempts to culti-

vate it by ordinary methods failed again and again. It had to be cultivated below the surface of certain nutrient media, or in a special atmosphere of nitrogen or hydrogen.

These and other difficulties for many years delayed the final proof of the true pathology of tetanus. The success of the work was mainly due to Nicolaier. He started from the well-known fact that tetanus mostly comes of wounds or scratches contaminated with particles of earth—such mischances as the grinding of dirt or gravel into the skin, or the tearing of it by a splinter of wood or a rusty nail; as Dr Poore says, in his Milroy Lectures (1899), "Every child who falls on the ground and gets an abrasion of the skin, all tillers of the soil who get accidental wounds in the course of duty, and every horse which 'breaks its knees' by falling in the London streets, runs potentially a risk of inoculation with tetanus." Nicolaier therefore studied the various microbes of the soil, and made inoculations of garden-mould under the skin of rabbits. He was able, by these inoculations, to produce tetanus in them; and the discharge from the points of inoculation, put under the skin of other rabbits, produced the disease again. He also identified the bacillus, and cultivated it; but in these cultures it was mixed with other organisms, and he failed to isolate it from them. Carle and Rattone, and Rosenbach, were able to produce tetanus in animals by inoculating them with discharge from the wounds of patients attacked by the disease. Finally, Kitasato, in 1889, found a

way of obtaining pure cultures of the bacillus. Beginning with impure cultures such as Nicolaier had made, he kept these at a temperature of 36° C. till the bacillus had spored ; then, by repeated exposures of the cultures to a temperature of 80° C. for three-quarters of an hour at a time, he killed-off all organisms except the spores of the tetanus-bacillus ; then he kept these in an atmosphere of hydrogen, at a temperature of 20° C., and thus got pure cultures.

Brieger, Fränkel, Cohen, Sidney Martin, Kanthack, and others, have studied the chemical products of the disease, have obtained them from cultures and from infected tissues, and have been able with these toxins to produce the disease in animals. As with the other infective diseases, so with tetanus, there have been two main lines of researches ; the one, toward a fuller knowledge of the chemical changes in the blood and in the central nervous system ; the other, toward a fuller knowledge of the nature and ways of the bacillus, and its method of invasion. Before any study of immunity or immunisation, or of neutralisation of the toxins in man by an antitoxin, came the study of the toxins and of the bacillus. It was proved, by an immense quantity of hard work, that the bacillus does not tend to invade the blood, or to pass beyond the lymphatic glands in the immediate neighbourhood of the site of inoculation ; that it stays in and about the wound, and there multiplies, and from this site pours into the blood the chemical products which cause the disease ; and

that these chemical substances have a selective action on certain nerve-cells in the brain and the spinal cord. This is the bare outline of the facts; and no account can be given here of the intricate problems of bacteriology and animal chemistry that have been answered, or are still waiting an answer. At least, it is evident that the whole pathology of tetanus was found, proved, and interpreted by the help of experiments on animals; and that these alone did away with the old false doctrine that the disease was due to rapid extension of inflammation up a nerve to the brain.

In 1894 came the use of an antitoxin in cases of the disease, and in 1895 42 cases were reported, with 27 recoveries. It cannot be said that any one of the diverse preparations of tetanus antitoxin, up to this present time, has triumphed over the disease. Tetanus is of all diseases the hardest to reckon with: the first sign of it is the last stage of it; there is no warning, nothing, it may be, but a healed scratch, till the central nervous system is affected with sudden and rapidly advancing degeneration of certain cells. These and other difficulties have stood in the way of an antitoxin treatment; and there is no less difficulty in estimating the efficacy of that treatment. The recovery, under antitoxin, of a "chronic" case cannot always or altogether be attributed to the treatment; and in a very acute case, antitoxin, like everything else, has but small chance of success. Various reports on the antitoxin treatment,

published during 1897-1899, give the following figures :—

26	cases, with	12	recoveries.
98	„	57	„
36	„	25	„
22	„	11	„
51	„	36	„
10	„	7	„

Probably the paper by Dr Lambert of New York, in the *Medical News*, July 1900, gives fairly the general opinion of the treatment, so far as the subcutaneous administration of antitoxin is concerned :—

"To judge the results of any treatment, we must compare statistics of any disease, before this treatment was used, with the statistics after its use. The death-rate of tetanus is variously given in acute cases from 78 to 96.6 per cent. ; in chronic cases, from 17.8 to 55 per cent. Cases reported in literature are usually reported because of some peculiarity connected with the course or origin of the disease. Hence, cases of acute tetanus that recovered would be reported because it was unusual for them to recover ; and cases that died would not be reported. Hospital statistics, therefore, which simply record the disease and its results, will give a fairer estimate of the true mortality of the disease. Behring reports the statistics of 716 such cases with a mortality of 88 per cent. I have previously reported 1222 war cases with a mortality of 88.6 per cent., and 280 cases occurring in time of peace with 76 per cent. mortality ; but these last cases seem to be open to the same doubt as expressed above. My own personal experience with 35 cases,

acute and chronic, in the hospitals of New York City, gives a mortality of 83 per cent. in time of peace. The fairest estimate seems to be, for acute cases, at least 88 per cent., and for the sub-acute and chronic cases, 40 per cent.

"The prognosis of tetanus is in direct ratio to the shortness of the incubation-period, and to the rapidity and intensity of the development of the symptoms. In judging of the results of antitoxin we must, therefore, divide the cases into *acute*, i.e., all those with an incubation-period of less than ten days, or with a longer incubation, but with very acute onset, and those with an unknown incubation, but with an acute course; and *chronic*, i.e., with more than ten days' incubation, or with a less than ten-day incubation, but with a slow, moderate onset of symptoms, and those with an unknown incubation and mild course. The following cases of tetanus, treated with antitoxin, comprise published and unpublished cases. We have a total of 279 cases, with a mortality of 44.08 per cent.: but of these we must rule out 17 cases—4 deaths from intercurrent diseases, 8 deaths in cases in which the antitoxin was given but a few hours before death, and 5 recoveries in which antitoxin was not given until after the twelfth day (as they probably would have recovered without it). We have left 262 cases, with 151 recoveries, and 111 deaths, a mortality of 42.36 per cent. Dividing the cases into acute and chronic, we have 124 acute cases, with 35 recoveries and 89 deaths, a mortality of 71.77 per cent., and 138 chronic cases, with 116 recoveries and 22 deaths, a mortality of 15.94 per cent. In interpreting critically these statistics, we see that in acute cases the mortality is but slightly reduced, being but 72 per cent. instead of 88 per

cent. But, in the less acute cases, there is a decided improvement, from 40 per cent. to 16 per cent. Taking the statistics as a whole, there is a distinct improvement in the mortality of tetanus since the introduction of antitoxin."

It would be foreign to the present purpose to pursue this matter further; for the other treatments, used by Baccelli and by Krokiewicz, and the subdural use of antitoxin, are also founded on experiments on animals; and the same will be true of any better method that shall be developed out of them.

The *preventive* use of the tetanus-antitoxin, for the immunisation of human beings or of animals, has given excellent results. Horses are very apt to be infected by tetanus; and the antitoxin has been used in veterinary practice, both for prevention and for cure. The curative results are not, at present, very good. But, as regards protection against the disease, there is evidence that horses can be immunised against tetanus by the antitoxin with almost mechanical accuracy. In some parts of the world, the loss of horses by tetanus is so common that their immunity is a very important matter; and that the antitoxin does confer immunity on them is shown by statistics from France and from the United States:—

1. *France.*—"The results of Nocard's method of preventive inoculations in veterinary practice are most striking. Among 63 veterinarians, there have been inoculated 2737 animals with preventive

doses of antitoxin, and not a single case of tetanus developed; while during the same period, in the same neighbourhoods, 259 cases of tetanus developed in non-inoculated animals." (*Med. News*, 7th July 1900.)

2. *United States.*—"Joseph MacFarland and E. M. Ranck, in addition to a synopsis of the method of manufacture of tetanus-antitoxin, give some facts of interest and importance in regard to its use for prophylaxis and treatment. The studies were made upon several hundred horses used for the production of various immunised serums in one of the large laboratories of the United States. The horses, because of the constant manipulations, frequently became infected with tetanus, and in 1897 and 1898, when scrupulous cleanliness and disinfection were the only precautions employed to prevent the disease, the death-rate varied from 8 to 10 per cent. During 1899 nearly two hundred horses were subjected to systematic immunisation with tetanus-antitoxin; and, in spite of otherwise similar conditions, the death-rate descended to 1 per cent." (*Medical Annual*, 1901.)

The preventive use of the antitoxin has, of course, a very limited range outside veterinary surgery. Tetanus, thanks to the use of antiseptic or aseptic methods, not only in hospital surgery but also in amateur and domestic surgery, has become a very rare disease, except in tropical countries. It is no longer a "hospital disease"; and, even in war, it no longer has anything like the frequency that it had, for instance, in the War of the Rebellion. A student may now go all his time at a large hospital without seeing more than one or two cases. But,

now and again, attention is called to some wholly unsuspected risk of the disease. For example, certain cases of tetanus occurred in Dundee among workers at the jute-mills there :—

"The last victim was a female worker in the jute-mill, who, six days after a crushed and lacerated wound of the foot, developed tetanus and died within twenty-four hours. Some of the dust, taken from under the machine in which the foot was crushed, was found to contain an unusually large number of tetanus-bacilli. The source of the jute used is India." (*Medical News*, August 1900.)

Again, at the Gebaer Anstalt at Prague, in 1899, an outbreak of tetanus occurred, with several deaths; but it was stopped when a preventive dose of the antitoxin was given to the new patients on admission.

Again, an amazing number of deaths from tetanus, in the United States, are due to wounds of the hands with toy-pistols. It is said that after the Fourth of July festivities in 1899, no less than 83 cases of tetanus were reported, 26 of them in and around New York. Almost all of them were due to gunshot wounds of the hand with toy-pistols: the unclean wad of the cartridge, made of refuse paper picked up in the streets, penetrates deep into the tissues of the hand, taking the germs of the disease with it, out of the reach of surgical disinfection. These cases of tetanus in the United States from toy-pistol wounds are so frequent, that immunisation has been recommended for them.

The *Medical News*, 1st June 1901, has the following note:—"H. G. Wells states that tetanus is endemic in Chicago, the specific organism being present in the dirt of the streets. Every Fourth of July an epidemic occurs, because these bacilli are carried deeply into wounds before wads from blank cartridges. . . . The writer thinks that such cases should receive a prophylactic dose, say, 5 c.c. of tetanus antitoxin, as soon as possible after the wound is first seen. It seems certain that if antitoxin prophylaxis were adopted, there would be no further Fourth of July epidemics, and this end would justify the means."

Again, a man might receive a lacerated wound under conditions especially favourable to infection: he might tear his hand in a stable where horses had died of tetanus, or he might cut his finger while he was working at the disease in a pathological laboratory, or he might receive a poisoned arrow-wound out in Africa. In any such emergency, he could safeguard his life with a protective dose of the antitoxin.

It remains to be added, that the modern study of tetanus has brought into more general use the old rule that the wounded tissues in a severe case of tetanus should be at once excised. Before Nicolaier's work, while the theory still survived that the disease was due to ascending inflammation of a nerve, this rule was neither enforced nor explained.

VI

RABIES

PASTEUR'S study of rabies began in 1880; and the date of the first case treated — Joseph Meister, a shepherd-boy of Alsace—is July 1885. The first part of the work was spent in a prolonged search for the specific microbe of rabies. It was not found: its existence is a matter of inference, but not of observation. In his earlier inoculations, Pasteur made use of the saliva of rabid animals; and M. Valléry-Radot tells the story, how Pasteur took him on one of his expeditions:—

"The rabid beast was in this case a huge bull-dog, foaming at the mouth and howling in his cage. All attempts to induce the animal to bite, and so infect one of the rabbits, failed. 'But we *must*,' said Pasteur, 'inoculate the rabbits with the saliva.' Accordingly a noose was made and thrown, the dog secured and dragged to the edge of the cage, and his jaws tied together. Choking with rage, the eyes bloodshot, and the body convulsed by a violent spasm, the animal was stretched on a table, and kept motionless, while Pasteur, leaning over his foaming head, sucked up into a narrow glass tube some drops of the saliva."

But these inoculations of saliva sometimes failed to produce the disease; and, when they succeeded, the incubation-period was wholly uncertain: it might be some months before the disease appeared. Thus Pasteur was led to use, instead of the saliva, an emulsion of the brain or spinal cord; because, as Dr Duboué had suggested, the central nervous system is the chief seat, the *locus electionis*, of the virus of rabies. But these inoculations also were not always successful, nor did they give a definite incubation-period.

Therefore he followed with rabies the method that he had followed with anthrax. As he had cultivated the virus of anthrax, by putting it where its development could be watched and controlled, so he must put the virus of rabies in the place of its choice. It has a selective action on the cells of the central nervous system, a sort of affinity with them; they are, as it were, the natural home of rabies, the proper nutrient medium for the virus: therefore the virus must be inoculated not under the skin, but under the skull.

These sub-dural inoculations were the turning-point of Pasteur's discovery. The first inoculation was made by M. Roux:—

"Next day, when I informed Pasteur that the intracranial inoculation offered no difficulty, he was moved with pity for the dog. 'Poor beast, his brain is doubtless injured: he must be paralysed.' Without reply I went down to the basement to fetch it, and let it come into the laboratory. Pasteur did not like dogs, but when he saw this

one, full of life, inquisitively rummaging about in all directions, he exhibited the greatest delight, and lavished most charming words upon it."

Henceforth all uncertainty was at an end, and the way was clear ahead: Pasteur had now to deal with a virus that had a definite period of incubation, and a suitable medium for development. The central nervous system was to the virus of rabies what the test-tube was to the virus of fowl-cholera or anthrax. As he had controlled these diseases, had turned them this way and that, attenuated and intensified them, so he could control rabies. By transmitting it through a series of rabbits, by sub-dural inoculation of each rabbit with a minute quantity of nerve-tissue from the rabbit that had died before it, he was able to intensify the virus, to shorten its period of incubation, to fix it at six days. Thus he obtained a virus of exact strength, a definite standard of virulence, *virus fixe*: the next rabbit inoculated would have the disease in six days, neither more nor less.

As he was able to intensify the virus by transmission, so he was able to attenuate it by gradual drying of the tissues that contained it. The spinal cord, taken from a rabbit that has died of rabies, slowly loses virulence by simple drying. A cord dried for four days is less virulent than one that has been dried for three, and more virulent than one dried for five. A cord dried for a fortnight has lost all virulence: even a large dose of it will not produce the disease. By this method of drying.

Pasteur was enabled to obtain the virus in all degrees of activity: he could always keep going one or more series of cords, of known and exactly graduated strengths, according to the length of time they had been dried—ranging from absolute non-virulence through every shade of virulence.

And, as with fowl-cholera and anthrax, so with rabies; a virus which has been attenuated till it has been rendered innocuous, can yet confer immunity against its more virulent forms: just as vaccination can protect against small-pox. A man, bitten by a rabid animal, has at least some weeks of respite before the disease can break out; and, during that time of respite, he can be immunised against the disease, while it is still dormant: he begins with a dose of virus attenuated past all power of doing harm, and advances day by day to more active doses, guarded each day by the dose of the day before, till he has manufactured within himself enough antitoxin to make him proof against any outbreak of the disease.

The cords used for treatment are removed from the bodies of the rabbits, by an aseptic method, and are cut into lengths and hung in glass jars, with some chloride of calcium in them, for drying. The jars are dated, and then kept in glass cases in a dark room at a constant temperature. To make sure that the cords are aseptic, a small portion of each cord is sown on nutrient jelly in a test-tube, and watched, to see that no bacteria occur in the tube. For each injection, a certain small quantity of cord is rubbed-up in sterilised fluid; and these

subcutaneous injections give no pain or malaise worth considering.

Of course, the treatment is adjusted to the gravity of the case. A bite through naked skin is more grave than a bite through clothing; and bites on the head or face, and wolf-bites, are worst of all. The number and character of the scars are also taken into account. An excellent description of the treatment, by a patient, was published in the *Birmingham Medical Review* of January 1898. It gives the following tables of treatment:—

1. *Ordinary Treatment.*

Day of Treatment.	Days of Drying of Cord.	Day of Treatment.	Days of Drying of Cord.
1	14 and 13	9 (½ dose)	3
2	12 and 11	10 (full dose)	5
3	10 and 9	11	5
4	8 and 7	12	4
5	6	13	4
6	6	14 (½ dose)	3
7	5	15 (full dose)	3
8	4		

2. *Cases of Moderate Gravity.*

Same treatment, up to 13th day.

Day of Treatment.	Days of Drying of Cord.	Day of Treatment.	Days of Drying of Cord.
14	3	17 (½ dose)	3
15	5	18 (full dose)	3
16	4		

3. *Grave Cases.*

Same treatment, up to 10th day.

Day of Treatment.	Days of Drying of Cord.	Day of Treatment.	Days of Drying of Cord.
11	4	17 (½ dose)	3
12	3	18 (full dose)	3
13	5	19	5
14	5	20	3
15	4	21	4
16	4	22	3

4. *Very Grave Cases.*

Same treatment as 3, and in addition.

Day of Treatment.	Days of Drying of Cord.	Day of Treatment.	Days of Drying of Cord.
23	5	25 (½ dose)	3
24	4	26 (full dose)	3

Furious criticism, unbelief, and flagrant misstatement of facts began at once, and lasted more than two years. Of Pasteur's opponents, the chief was M. Peter, who besought the Académie des Sciences, about once a week, that they should close Pasteur's laboratory, because he was not preventing hydrophobia but producing it. The value of M. Peter's judgment may be estimated by what he had said, a few years earlier, about bacteriology in general—"I do not much believe in that invasion of parasites which threatens us like an eleventh plague of Egypt. After so many laborious researches, nothing will be changed in medicine, there will only be a few more microbes. M. Pasteur's excuse is that he is a chemist, who has tried, out of a wish to be useful, to reform medicine, to which he is a complete stranger."

But it does not matter what was said seventeen years ago. In England, the Report of the 1886 Committee, and the Mansion House meeting in July 1889, mark the decline and fall of all intelligent opposition to the work. Among so many thousand cases, during so many years, it would be a miracle indeed if not a single case had failed or gone amiss; but we are concerned here with the thou-

sands. Take, to begin with, four reports from Athens, Palermo, Rio, and Paris. It is to be noted that the patients, alike at Paris and at other Institutes, are divided into three classes :—

"A. Bitten by animals proved to have been rabid by the development of rabies in other animals inoculated from them.

"B. Bitten by animals proved to have been rabid by dissection of their bodies by veterinary surgeons.

"C. Bitten by animals suspected to have been rabid."

It is to be noted also, as a fact proved beyond doubt, that the full benefit of the treatment is not obtained at once; the highest degree of immunity is reached about a fortnight after the discontinuance of the treatment. Those few cases, therefore, where hydrophobia has occurred, not only in spite of treatment, but within a fortnight of the last day of treatment, are counted as cases where the treatment came too late.

Finally, what was the risk from the bite of a rabid animal, in the days before 1885? It is a matter of guess-work. One writer, and one only, guessed it at 5 per cent.; another guessed it at 55, and a third came to the safe conclusion that it was "somewhere between these limits." Leblanc, who is probably the best guide, put it at 16; and Pasteur himself put it between 15 and 20. But suppose it were only 10; that, before Pasteur, out of every 100 men bitten by rabid animals, 90 would escape and only 10 would die of hydrophobia; then take this fact,

that in one year, at one Institute alone, there were 142 patients in class A, bitten by animals that were proved, by the unanswerable test of inoculation, to have been rabid; and 1 death. And every year the same thing; and in all the twelve years together, 2872 such cases (A) and 20 deaths—a mortality not of 10 per cent., but of less than 1 per cent.

1. *Athens.*

The *Annales de l'Institut Pasteur*, June 1898, contain Dr Pampoukis' report of three years' work at the Hellenic Institute, from August 1894 to December 1897. During this period 797 cases were treated—590 male and 207 female. The animals that bit them were—dogs, 732; cats, 34; wolf, 1; other animals, 13; and the 17 other patients had been exposed to infection from the saliva of hydrophobic patients. Of the 797 cases, 245 were of class A, 112 B, and 440 C.

"Among the 797 persons treated, there are 2 deaths, one in class B and the other in class C. Thus the mortality has been 0.25 per cent. Besides these 2 who died of rabies there are 5 more, in whom the first signs of rabies showed themselves in less than fifteen days after the last inoculation.

"Finally, beside these 797 cases, there is 1 other case, bitten by a wolf, in which the treatment failed. If we reckon this last case in the statistics of mortality, we have 3 deaths in 798 cases= 0.37 per cent.

"Beside these 798 cases treated at the Institute,

there have been others that have not undergone the antirabic treatment, having trusted the assurances of those who are called in Greece *empirics*. Among these non-treated cases there are 40 who have died of rabies."

2. *Palermo.*

The *Annales* for April 1896 give the report by Dr de Blasi and Dr Russo-Travali of the work of the Municipal Institute at Palermo during $8\frac{1}{2}$ years, from March 1887 to December 1895. The number of cases was 2221; in 1240 (class A), the animals were proved to have been rabid by the result of inoculations; in 981, there was reason to suspect rabies.

"Setting aside 5 patients who died during the course of the treatment, and 5 others who died less than fifteen days after the end of the treatment, we have had to deplore only 9 failures = 0.4 per cent. Even if we count against ourselves the 10 other cases, the mortality is still only 0.85."

3. *Rio de Janeiro.*

The *Annales* for August 1898 give Dr Ferreira's report of ten years' work (February 1888 to April 1898) at the Pasteur Institute at Rio. The number of cases treated was 2647, of whom 1987 were male and 660 female. Beside these 2647 there were 1234 who were not treated, because it was ascertained that they were in no danger of rabies; 3 who were brought to the Institute, already suffering from the disease; and 59 who refused treatment.

Of the 2647 persons treated, 10 had pricked their hands at work in the laboratory, 3 had exposed chance scratches on their hands to the saliva of rabid animals, and 1 had been bitten by a rabid patient. Of the rest, 1886 had been bitten on the bare skin, and 747 through clothing.

In 236 cases the rabies of the animal had been proved by inoculation. In 1173 it had been recognised by the signs of the disease. In 1238 there was good reason to suspect that the animal had been rabid.

Of the 2647 patients, in 30 cases the treatment was stopped, because the animals were at last traced, after treatment was begun, and were found not to be rabid. In 65 cases the patients, after treatment was begun, refused to go on with it, and 3 of them died of rabies. In 6 cases rabies developed during treatment; 5 of them had been very badly bitten about the head, and 1 did not come for treatment till the twenty-first day after the bite, and was attacked by rabies two days later. And 5 cases died of other maladies that had nothing to do with rabies. Setting aside these 106 cases, there remain 2541 cases, with 20 deaths = 0.78 per cent. But, of these 20 deaths, 9 occurred within fifteen days of the end of treatment, before protection was fully established. If these 9 deaths be excluded, the figures stand at 2532 cases, with 11 deaths = 0.43 per cent.

4. *Paris.*

Dr Pottevin's report on the work of the Pasteur Institute (Paris) during 1897 (*Annales*, April 1898) must be given word for word, without abbreviation.

I.

During 1897, 1521 patients received the anti-treatment at the Pasteur Institute: 8 died of rabies. The notes of their cases will be found at the end of this paper.

If we exclude 2 of these 8 cases—the cases of Heniquet and Morin, where death occurred before it was possible for the vaccinations to produce their effect—the results of the vaccinations in 1897 are—

Patients treated . . .	1519
Deaths	6
Mortality per cent. . . .	0.39

In the following table these figures are compared with those of preceding years :—

Year.	Patients treated.	Deaths.	Mortality per cent.
1886	2671	25	0.94
1887	1770	14	0.79
1888	1622	9	0.55
1889	1830	7	0.38
1890	1540	5	0.32
1891	1559	4	0.25
1892	1790	4	0.22
1893	1648	6	0.36
1894	1387	7	0.50
1895	1520	5	0.33
1896	1308	4	0.30
1897	1521	6	0.39

II.

Patients treated at the Pasteur Institute are divided into three classes, as follows :—

A. The rabies of the animal was proved by experiment, by the development of rabies in animals inoculated with its bulb (the upper end of the spinal cord).*

B. The rabies of the animal was proved by veterinary examination (dissection of its body).

C. The animal was suspected of rabies.

We give here the patients treated in 1897, under these three classes :—

	Bites of the Head.			Bites on the Hands.			Bites of the Limbs.			Total.		
	Patients.	Deaths.	Mortality per cent.	Patients.	Deaths.	Mortality per cent.	Patients.	Deaths.	Mortality per cent.	Patients.	Deaths.	Mortality per cent.
A	15	0	0	81	0	0	46	1	2.1	142	1	0.7
B	106	0	0	539	4	0.74	273	1	0.4	918	5	0.65
C	30	0	0	244	0	0	187	0	0	461	0	0
	151	0	0	864	4	0.46	506	2	0.4	1521	6	0.39

The following tables, giving the results obtained since the vaccinations were first used, show that the gravity of the bites varies with their position on the body, and that the mortality is always below 1 per

* It is satisfactory to know that rabbits affected with rabies do not suffer in the same way as dogs and some other animals, but become subject to a painless kind of paralysis.

cent. among patients bitten by dogs undoubtedly rabid :—

	Patients.	Deaths.	Mortality.		Patients.	Deaths.	Mortality.
Bites of the Head.	1,759	21	1.1	A	2,872	20	0.69
Bites of the Hands	11,118	53	0.47	B	12,547	61	0.48
Bites of the Limbs	7,289	22	0.30	C	4,747	15	0.31
	20,166	96	0.46		20,166	96	0.46

III.

In regard to their nationality, the 1521 patients treated at the Pasteur Institute in 1897 were as follows :—

Germany . . .	8	United States . .	1
England . . .	83	Greece . . .	1
Belgium . . .	14	India . . .	33
Egypt . . .	2	Switzerland . .	33

That is, 175 foreigners and 1346 French.

IV.

Notes of the eight cases where the treatment failed :—

1. Camille Bourg, 26. Bitten 11th April ; treated at the Pasteur Institute, 13th to 30th April ; died of rabies at the Lariboisière Hospital, 26th May, Six penetrating bites on the ball of the left thumb. The dog was examined by M. Grenot, a veterinary surgeon at Paris, and the dissection gave evidence of rabies. Another person bitten and treated at the same time as Bourg is now in good health.

2. Louis Fiquet, 23. Bitten 22nd April; treated at the Pasteur Institute, 23rd April to 10th May; died of rabies at the Necker Hospital, 4th June. Five bites, two of them deep, round the right thumb. They had been cauterised five hours after infliction. The dog was examined by M. Caussé, a veterinary surgeon at Boulogne, and the dissection gave evidence of rabies. Another person bitten at the same time as Fiquet is now in good health.

3. Annette Beaufort, 19. Licked on the hands, which were chapped, on 15th April. The dog was killed next day, examined, and declared to have been rabid by M. Lachmann, a veterinary surgeon at Saint-Étienne. Treated at the Pasteur Institute, 20th April to 7th May. Died of rabies 14th October. Two other persons bitten by the same dog and treated at the Pasteur Institute are now in good health.

4. Julien Heniquet, 53. Bitten 11th March, by a dog that M. Jenvresse, veterinary surgeon at Beaumont-sur-Oise, declared after dissection to have been rabid. One bite had torn the lower lip, the wound had been sutured; three other wounds on the nose. The wounds had not been cauterised. Treated at the Pasteur Institute, 18th May to 5th June. First symptoms of rabies showed themselves 4th June, before the treatment was finished; died 7th June. As the disease had its onset during the course of the inoculations, this case should be excluded from the number of those who died of rabies after treatment.

5. Germain Segond, 7. Penetrating bite on the bare right fore-arm, 23rd May. Cauterised an hour later with a red-hot iron. Treated 26th May to 9th June; died of rabies 22nd July. The dog's bulb had been sent to the Pasteur Institute. A

guinea-pig inoculated in the eye 26th May was seized with rabies 10th September.

6. Suzanne Richard, 8. Bitten 12th June on the left leg by a dog, found on dissection to have been rabid by M. Touret, veterinary surgeon at Sannois. The bite, penetrating 3 cm. long, had been sutured; it had been made through a cotton stocking, and had been cauterised in half an hour. Treated 13th to 30th June; died of rabies 2nd August. (Notes from M. le Dr Margny, at Sannois.)

7. Joseph Vaudale, 33. Bitten on the left hand, 8th August. Six penetrating bites on the back of the hand; had not been cauterised. The dog was declared rabid by M. Verraert, veterinary surgeon at Ostend. Treated at the Pasteur Institute, 11th to 28th August; died of rabies 27th September.

8. Paul Morin, 38. Bitten 24th August on the left cheek, a single bite, 2 cm. long; no cauterisation. The dog was sent to the Alfort School, 25th August, and found to be rabid. Treated at the Pasteur Institute, 26th August to 15th September. Died of rabies some days after the end of treatment (three weeks after the bite, says a note sent to us). The interval between the end of the treatment and the onset of the disease being less than fourteen days, Morin must not be counted in the number of patients inoculated under conditions which permit successful inoculation.

The reports of the Pasteur Institute at Paris, for 1898 and following years, are as follows :—

1898.

The number of patients treated was 1465, of whom 4 died of rabies: but one of these four died only ten days after treatment, and is therefore not to be counted against the efficacy of the treatment:—

"D'après les expériences faites sur les chiens, on est autorisé à penser que les centres nerveux des personnes mortes de rage dans les 15 jours qui suivent le traitement ont été envahis par le virus rabique avant que la cure ait pu avoir toute son efficacité."

Two patients were seized by rabies during treatment, and are not counted among those treated. The figures, therefore, are—

Cases treated	1465
Deaths	3
Mortality	0.2 per cent.

	Bites on the Head.			Bites on the Hands.			Bites on the Limbs.			Total.		
	Treated.	Died.	Mortality.	Treated.	Died.	Mortality.	Treated.	Died.	Mortality.	Treated.	Died.	Mortality.
Table A .	11	0	0	100	0	0	30	0	0	141	0	0
Table B .	80	0	0	549	1	0.18	226	0	0	855	1	0.11
Table C .	41	0	0	265	1	0.37	163	1	0.61	469	2	0.42
Total .	132	0	0	914	2	0.22	419	1	0.24	1465	3	0.20

A. La rage de l'animal mordeur a été expérimentalement constatée par le développement de la

maladie chez des animaux mordus par lui ou inoculés avec son bulbe.

B. La rage de l'animal mordeur a été constatée par examen vétérinaire.

C. L'animal mordeur est suspect de rage.

Of the 3 patients who died more than fifteen days after the treatment, 1 came from India (Lahore), bitten 22nd August, treated in Paris 12th September to 26th October, died in India 23rd November. "Son cas a donné lieu à certaines polémiques. Un journal anglais des Indes, *The Englishman*, a publié une dépêche d'après laquelle le chien qui avait mordu O'Leary serait encore vivant et en parfaite santé; ce fait nous a été signalé par un rapport de M. le consul général de France à Calcutta, que M. le ministre des affaires étrangéres a bien voulu nous communiquer; nous avons procédé à une enquête, et nous donnons ci-dessous un extrait d'une lettre qui nous a été addressée des Indes le 20 avril par le frère de O'Leary; il met les choses au point, 'Vous me demandez des renseignements sur le chien qui a mordu mon frère, on n'a pas retrouvé sa trace et aucun vétérinaire n'a pu l'examiner; à part mon pauvre frère, personne n'a vu ce chien, on n'a donc aucune preuve qu'il fût malade; mais en même temps que mon frère, il a mordu un petit chien à nous, celui-ci était encore vivant quand mon frère est mort, depuis on l'a abattu.'"

Of the 2 patients who died during treatment, 1 was a street-singer, bitten in thirteen places on the face and hands: "trois autres personnes

mordues par le même chien et traitées à l'Institut Pasteur sont actuellement en parfaite santé." The other was a child three years old, from Castleblarney, bitten on the face. The patient who died only ten days after treatment, was this child's brother, seven years old, bitten on the face, arm, and hand.

1899.

The number of patients treated was 1614, of whom 10 died of rabies: but of these, 4 died less than fifteen days after treatment, and 2 during treatment: these 6 deaths are not to be counted against the efficacy of the treatment. The figures, therefore, are :—

Cases treated 1614
Deaths 4
Mortality . . . . 0.25 per cent.

	Bites on the Head.			Bites on the Hands.			Bites on the Limbs.			Total.		
	Treated.	Died.	Mortality.	Treated.	Died.	Mortality.	Treated.	Died.	Mortality.	Treated.	Died.	Mortality.
Table A.	13	0	0	104	2	1.94	35	0	0	152	2	1.31
Table B.	142	1	0.70	664	0	0	293	1	0.34	1099	2	0.18
Table C.	33	0	0	194	0	0	136	0	0	363	0	0
Total .	188	1	0.53	962	2	0.30	464	1	0.23	1614	4	0.25

1900.

The number of patients treated was 1420, of whom 11 died of rabies; but of these, 6 died less than fifteen days after treatment, and 1 during treatment: these 7 deaths are not to be counted

against the efficacy of the treatment. The figures, therefore, are :—

Cases treated 1420
Deaths 4
Mortality . . . . 0.28 per cent.

	Bites on the Head.			Bites on the Hands.			Bites on the Limbs.			Total.		
	Treated.	Died.	Mortality.	Treated.	Died.	Mortality.	Treated.	Died.	Mortality.	Treated.	Died.	Mortality.
Table A .	20	0	0	109	3	2.75	50	1	2.00	179	4	2.23
Table B .	78	0	0	555	0	0	233	0	0	866	0	0
Table C .	28	0	0	188	0	0	159	0	0	375	0	0
Total .	126	0	0	852	3	0.35	442	1	0.22	1420	4	0.28

1901.

The number of patients treated was 1321, of whom 8 died of rabies; but of these, 3 died during treatment: these 3 deaths are not to be counted against the efficacy of the treatment. The figures, therefore, are :—

Cases treated 1318
Deaths 5
Mortality . . . . 0.38 per cent.

	Bites on the Head.			Bites on the Hands.			Bites on the Limbs.			Total.		
	Treated.	Died.	Mortality.	Treated.	Died.	Mortality.	Treated.	Died.	Mortality.	Treated.	Died.	Mortality.
Table A .	20	0	0	93	0	0	38	0	0	171	0	0
Table B .	80	0	0	521	4	0.77	184	0	0	785	4	0.51
Table C .	23	1	4.34	186	0	0	153	0	0	362	1	0.27
Total .	123	1	0.79	800	4	0.50	395	0	0	1318	5	0.38

It is not impossible that some sort of intensive modification of Pasteur's treatment may be found, not for the prevention, but for the cure of hydrophobia; and two successful cases of this kind have been reported in the *Annales* of the Paris Institute. Apart from this faint hope, the *cure* of hydrophobia is where it was in the days of the "Tonquin medicine" and the "Tanjore pills." As for the "Buisson Bath Treatment for the Prevention and Cure of Hydrophobia," it failed egregiously to afford the very least benefit to inoculated animals, and the evidence in its favour is just like the evidence for Mother Siegel's Syrup. Dr Buisson invented it because, having imagined that he had hydrophobia, he took a vapour-bath to kill himself: *and at* 42 *degrees* (127 *Fahrenheit*) *I was cured!* It was an ordinary case of fear of hydrophobia. Then there is "a mass of cures effected in Asia": we know that mass of cures in Asia; but only one of them is quoted, and in that case nothing is said about the dog. And there is the case of Pauline Kiehl, who was "refused treatment by M. Pasteur," which is certainly the strangest feature of the case; but it is not said where this case is published. Also, a native of Dacca, in India, testifies, "No fewer than thirty cases we treated successfully. One case, bitten by a cobra, we treated with wonderful success, and another by a rabid fox." He does not say whether the cobra was rabid. Also, a lady doctor, "in charge of the Temperance and Buisson Institute, Byculla, Bombay," gives the case of a little boy who was bitten by a dog "suspected,

though not proved, to be rabid"; and she says, "If this case be interpreted as one of tetanus rather than hydrophobia, it only indicates another important use for the Buisson Bath." *Interpreted* is good. The whole thing is arrant nonsense; and the Indian Government ought to note that this idiotic treatment is used alike for rabies, snake-bite, and (?) tetanus. It gives some comfort in some cases of cholera; but it cannot either protect or save life, either in that disease or in any other.

The *Annales* for May 1902 contain accounts of the work of the Institutes at Tunis and Bordeaux. At Tunis, between June 1894 and June 1901, 827 cases were treated, with 6 deaths, 2 of them during treatment and 1 ten days after treatment. Setting aside these 3 cases, there remain 3 deaths = 0.36 per cent. At Bordeaux, between May 1900 and May 1901, there were 100 cases without a death.

VII

CHOLERA

THE study of cholera was the hardest of all the hard labours of bacteriology; it took years of work in all parts of the world, and the difficulty and disappointments over it are past all telling. Koch's discovery of the comma-bacillus (1883) raised a thousand questions that were solved only by infinite patience, international unity for science, and incessant research; and the Hamburg epidemic (1892) marks the time when the comma-bacillus was at last recognised as the cause of cholera. A mere list of the men who did the work would fill page after page; it was bacteriology *in excelsis*, often dangerous,* and always laborious.

* "In order to prove that this *vibrio* is the cause of Asiatic cholera, several tests upon themselves have been voluntarily made by investigators in laboratories. Thèse were carried out in Munich and in Paris. The results to the experimenters were sufficiently severe to indicate positively the pathogenic character of the spirillum, and its capacity to produce cholera-like infections. Such experimentation is, of course, to be deprecated; indeed, the occurrence of accidental laboratory infections, one of which ended fatally, furnished the necessary final proof of the specificity of the cholera vibrio, and rendered unnecessary any exposure to the risks belonging to voluntary inoculation." (Dr Flexner, Stedman's *Twentieth Century Practice*, vol. xix., 1900.)

There is the same heroic note in the story of the preventive treatment of cholera by Haffkine's method; one of the men in whom Pasteur seems to live again. He began in 1889, under Pasteur's guidance, to study the immunisation of animals against the cholera-bacillus. Other men, of course, were working on the same lines—Pfeiffer, Brieger, Metchnikoff, Fischer, Gamaleïa, Klein, Wassermann, and many more—and by 1892 the immunisation of animals was proved up to the hilt. Then came the advance from animals to men, from laboratories to Indian cities, villages, and cantonments; and here the honour is Haffkine's, and his alone. Ferran's inoculations (Spain, 1885) had failed. Haffkine, having tested his method on himself and his friends, went to India, with a commendatory letter from the British Government:—

"Researches on cholera, with special reference to inoculation, were undertaken and carried on in my laboratory, in the Pasteur Institute in Paris, between 1889 and 1893. The experiments resulted in the elaboration of the present method, which when tried on animals was found to render them resistant against every form of cholera-poisoning otherwise fatal to them.

"The physiological and pathological effect on man was then studied on some sixty persons, mostly medical and scientific men interested in the solution of the problem. The effect was found to be harmless to health. The next step was to transfer the operations to the East." (Haffkine's *Report to the Government of India*, 1895.)

He reached Calcutta in March 1893, and at the request of Mr Hankin * was invited to Agra; here, in April, he vaccinated over 900 persons, including many English officers. From Agra to Aligarh; and from Aligarh he was asked to more places than he could visit. In 1895 his health failed, and no wonder; and he came back to Europe for a short time:—

"My actual work in India lasted twenty-nine months, between the beginning of April 1893 and the end of July 1895. During this period the anti-cholera vaccination has been applied to 294 British officers, 3206 British soldiers, 6629 native soldiers, 869 civil Europeans, 125 Eurasians, and 31,056 natives of India. The inoculated people belonged to 98 localities in the North-West Provinces and Oudh, in the Punjab, in Lower Bengal and Behar, in the Brahmaputra valley, and in Lower Assam. No official pressure has been brought on the population, and only those have been vaccinated who could be induced to do so by free persuasion. In every locality, efforts were made to apply the operation on parts of large bodies of people living together under identical conditions, in order to compare their resistance in outbreaks of cholera with that of non-inoculated people belonging to the same unit of population. This object has been obtained in 64 British and native regiments, in 9 gaols, in 45 tea-estates, in the fixed agricultural population of the villages parallel to Hardwâr pilgrim road, in the

* Mr Hankin, whose name is had in remembrance by Cambridge men, is Chemical Examiner and Bacteriologist to the North-West Provinces and Oudh, and to the Central Provinces.

bustees of Calcutta, in a certain number of boarding-schools, where the parents agreed to the inoculation of their children, in orphanages, etc. The vast majority of inoculated people lived thus under direct observation of the sanitary and medical authorities of India." (Haffkine, Lecture in London. *British Medical Journal*, 21st Dec. 1895.)

Altogether, upwards of 70,000 injections on 42,179 people—*without having to record a single instance of mishap or accident of any description produced by our vaccines.* Consider the colossal difficulties of this new treatment: the frequent running short of the vaccine, preventing a second injection; the absolute necessity, at first, of using very small doses of a weak vaccine, lest one disaster should occur; the impossibility of avoiding, now and again, some loss of strength in the vaccine; the impossibility of knowing how long the protection would last. Surely in all science there is nothing to beat this first voyage of adventure single-handed to fight the cholera in India.

Later than Haffkine's 1895 report, we have Dr Simpson's 1896 report: "*Two Years of Anti-choleraic Inoculations in Calcutta.* By W. J. Simpson, M.D., M.R.C.P., D.P.H., Health Officer, Calcutta." The date of this report is 8th July 1896; and it gives not only the Calcutta results, but all that are of any use for exact judgment:*—

* For a summary of this report, see the *Lancet*, 8th August 1896. For more recent results, see Surgeon-Captain Vaughan and Assistant-Surgeon Mukerji, in the thirtieth annual report

"The results of Calcutta are fully confirmed by those obtained in other parts of India, wherever it was possible to make all the necessary observations with precision, and wherever the cases were sufficiently numerous to show the effect of the inoculation.

"Outside Calcutta, since the commencement of the inoculations in India in April 1893, opportunities for an exact comparison of the respective powers of resistance against cholera of inoculated and non-inoculated persons presented themselves; (1) in Lucknow, in the East Lancashire Regiment; (2) in Gaya, in the jail; (3) in Cachar, among the tea-garden coolies; (4) in Margherita, among coolies of the Assam-Burmah Railway Survey; (5) in Durbhanga, in the jail; (6) in the coolie camp at Bilaspur, (7) in Serampur, among the general population."

Here, then, in this 1896 report, are all the results that give an answer to the question, What will happen when cholera breaks out among a number of people living under the same conditions, of whom some have received preventive treatment, and the rest have been left to Nature?

1. *Calcutta* (1894-1896).

"The number of people inoculated during the period under review was 7690; of these, 5853 are Hindus, 1476 Mahomedans, and 361 other classes. . . . Considering that the system is a new one, that the inoculations are purely voluntary, and everything

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of the Sanitary Commissioner for Bengal (1897). Also the note published by Surgeon-Captain Nott, in the *Indian Medical Gazette*, May 1898.

connected with them has to be explained before the confidence of the people can be obtained, and considering how long new ideas are in taking root among the general population—and in this case it is not merely the acceptance of an idea, but such faith in it as to consent to submit to an operation—the number is certainly satisfactory for a beginning. The present problem can be compared with the introduction of vaccination against small-pox into Calcutta. It took 25 years before the number of vaccinations reached an average of 2,000; whereas the inoculations against cholera have in two years nearly doubled that average. This is a proof that, in spite of the difficulties which every new movement naturally has to meet with, there are large numbers of people anxious to avail themselves of the protective effect of the inoculations.

"Although all sorts and conditions of individuals, weak and strong, sickly and healthy, young and old, well nourished and badly nourished, and often persons suffering from chronic diseases, have been inoculated, in every instance, without exception, the inoculations have proved perfectly harmless.

"The investigations on the effect of the inoculation are made exclusively in those houses in which cholera has actually occurred, the object being to ascertain and compare the incidence of cholera on the inoculated and not inoculated in those houses in which inoculations had been previously carried out. *For this purpose, affected houses in which inoculations have not been performed, and inoculated houses in which cholera has not appeared, are excluded.*"

Nature gave a demonstration in 77 houses. In one house, and one only, all the household had been

inoculated; in 76, inoculated and non-inoculated were living together; but of these 76 houses, 6 are excluded from the table of results, because the inoculated in them were so few—less than one-tenth of the household—that their escape from cholera might be called chance. The cholera came, and left behind it this fact:—

654 uninoculated individuals had 71 deaths
= 10.86 per cent.
402 inoculated in the same households had
12 deaths = 2.99 per cent.

If we add the 6 houses which Dr Simpson excludes, we find that in 77 houses there were 89 deaths from cholera, 77 being among the uninoculated and 12 among the inoculated.

Moreover, of these 12 deaths, 5 occurred during the first five days after inoculation—that is to say, during the period in which the protective influence of the vaccine was still incomplete. *Then came a period of more than a year, during which the uninoculated had* 42 *deaths, and the inoculated had one death.* The remaining 6 of the 12 deaths occurred more than a year after inoculation, and 5 of these 6 had received only one inoculation of the weak vaccine that was used early in 1894.

Take a good instance that came at the very beginning of the work:—

"A local epidemic took place around two tanks in Kattal Began *bustee*, ward 19, occupied by about 200 people. In this *bustee*, about the end of March,

2 fatal cases of cholera and 2 cases of choleraic diarrhœa occurred. The outbreak led to the inoculation of 116 persons in the *bustee* out of the 200. Since then, 9 cases of cholera, of which 7 were fatal, and 1 case of choleraic diarrhœa have appeared in the *bustee*, and it is a very extraordinary fact that all these 10 cases of cholera have occurred exclusively among the uninoculated portion of the inhabitants, which, as stated, forms the minority in the *bustee;* while none of the inoculated have been affected." (*Cholera in Calcutta in* 1894. W. J. Simpson.)

2. *Lucknow* (1893).

The story of the outbreak of cholera in the East Lancashire Regiment must be read carefully :—

"Rumour magnified the events connected with this outbreak, and distorted the facts connected with the inoculations; and as a result, the current of public opinion, which had previously been in favour of inoculation, set-in strongly in the opposite direction. The advocates of anti-choleraic inoculations were abused in no particularly measured terms, and the inoculations were held up to be the source of every possible evil and danger . . . of the most loathsome diseases, and of every ill which man is heir to. The distrust engendered by these misrepresentations and fulminations was, however, only of a temporary nature; and when the exact circumstances came to be known and understood, the confidence created by the Calcutta experience began to be considerably restored. Inoculations were performed in May 1893, in the East Lancashire, Royal Irish, 16th Lancers, 7th Bengal Infantry, 7th Bengal Cavalry, and general populations in the

Civil Lines. In 1894, cholera appeared among the native population of Lucknow, in the form of an epidemic distinguished by its extreme virulence, patients succumbing in the course of a few hours. It is stated that the epidemic was of a most malignant type. In the latter part of July it entered the cantonments, and attacked the East Lancashire, almost exclusively confining its ravages to that regiment."

In the East Lancashire, 185 men were inoculated in May 1893. From the statistical returns obtained from the military authorities at Lucknow, it appears that at the time of the outbreak, in July 1894, the strength of the men, including those in hospital, was 773; and, of these, 133 had been inoculated, as recorded in the inoculation register, and 640 had not been inoculated.

The following table shows the total number of attacks and deaths in not inoculated and inoculated:—

	Attacks.	Deaths.
	Per cent.	Per cent.
Non-inoculated, 640 .	120 = 18.75	79 = 12.34
Inoculated . 133 .	18 = 13.53	13 = 9.7

The men were moved into camp; but this movement seemed only to make things worse: "the epidemic in the camp appears to have been twice as severe as in the cantonment."*

* "The moving into camp, notwithstanding this example, is all the same an excellent measure of defence, and would with reason be adopted in every outbreak." (Simpson, *loc. cit.*)

Lucknow came so early in the work of inoculation, that weak vaccines were used in small doses. The cholera, when it broke out, was "of a most malignant type, senior medical officers of long experience in the country stating that such a virulent cholera had not been seen by them for very many years past." More than a year had elapsed between the inoculations and the outbreak of the cholera. It is no wonder that the regiment was not well protected :—

"The small amount of protection which the inoculations afforded in this case may have depended on the mild effects which the injections produced on the men at the time of the operation in 1893, in comparison with the severity of the epidemic which attacked the regiment. It is recorded in the Lucknow Inoculation Registers that only in two men, out of the 185 inoculated in 1893, a marked febrile reaction was obtained; in 77 individuals the vaccinal fever was only slight, while in 66 there was no reaction: an effect which was due to the weakness of the vaccines procurable at that period of work, and to the small doses used. The influence of the vaccines was possibly further reduced, at the time of the epidemic, by a lapse of fourteen to fifteen months." (Haffkine, 1895 Report.)

3. *Gaya Jail.*

On 9th July 1894, an outbreak of cholera occurred in the Gaya jail, and by 18th June there had been 6 cases and 5 deaths. On that day and the next day, 215 prisoners were inoculated. The average number of the prisoners during the outbreak was

207 inoculated, and 202 not inoculated. Surgeon-Major Macrae, superintendent of the jail, reports :—

"The inoculations being purely voluntary, no selection of prisoners was possible, but all classes of the jail were represented—male and female, old and young, habituals and less frequent offenders, strong and weakly, convalescent and even hospital patients sent their representatives; no difference of any kind was made between inoculated and non-inoculated; they were under absolutely identical conditions as regards food, water, accommodation, etc., in fact in every possible respect."

Of course, the best results could hardly be obtained, because the cholera was already at work: it took about ten days for the 1894 vaccine to produce its full effect; and two inoculations were generally made, one five days after the other. This gradual action of the vaccine is well shown in Dr Simpson's table :—

	Non-Inoculated, 202.		Inoculated, 207.	
	Cases.	Deaths.	Cases.	Deaths.
During 5 days after 1st inoculation	7	5	5	4
During 3 days after 2nd inoculation	5	3	3	1
After 3 days after 2nd inoculation	8	2	0	0
Total	20	10	8	5

Haffkine's comment on these figures must be noted here :—

"In the Gaya jail, the inoculations were *for the*

first time applied *in a prevalent epidemic*, and *very weak doses* of a relatively weak vaccine were used. . . . Far higher results have been obtained by an application of stronger doses. In the *bustees* situated round the tanks in Calcutta, where cholera exists in a permanent state, the disease occurred in 36 houses with inoculated people. In each of these houses there was one part of the family inoculated and another not. The observations were continued for 459 days, with the following results :—

During the first period of 5 days, subsequent to the inoculation with first vaccine, cholera occurred in 8 houses.

75 non-inoculated had 5 cases, with 3 deaths.
52 inoculated had 3 cases, with 3 deaths.

During the second period of 5 days, subsequent to the second inoculation, cholera occurred in 2 houses.

8 non-inoculated had 2 cases, with 2 deaths.
17 inoculated had no cases.

After the 10 *days necessary for the preventive treatment had expired, and up to the* 459*th day, the disease visited* 26 *houses.*

263 *non-inoculated had* 38 *cases, with* 34 *deaths.*
137 *inoculated had* 1 *case, with* 1 *death, in a child that had not been brought up for the second inoculation.*"

4. *Assam-Burmah Railway.*

For a good instance of lives saved even during an outbreak, take the Assam-Burmah Railway coolies :—

"Three hundred and fifty * Khassia Hill coolies had been collected for the survey party of the Assam-Burmah Railway, and put under the escort of a detachment of Goorkhas, when cholera broke out amongst them. The largest part of the coolies immediately submitted to the preventive inoculation, the rest remained uninoculated. The result was that *among the not-inoculated minority there were* 34 *cases, with* 30 *deaths; whereas the inoculated had* 4 *fatal cases.*" (Haffkine, 1895, Lecture in London.)

5. *Durbhanga Jail* (1896).

The figures in this instance are small: but Surgeon-Captain E. Harold Brown's report is very pleasant reading. Cholera broke out in the jail on 31st March 1896, and by 9th April there had been 8 cases. Next day, 172 prisoners were moved into camp 12 miles away; and 53 were left behind, the sick in the jail hospital, the patients in the cholera huts, with their attendants, the old and infirm, and a few cooks and sweepers. That day, 3 cases occurred in the camp, and 1 in the jail; and on the 11th, at 2 and 4 A.M. 2 more cases were

* The exact number is 355, of whom 196 were inoculated; the coolies numbered 343, and the Goorkhas 12. (See Dr Simpson's 1896 Report.)

reported in camp. At 7.30 A.M., Haffkine and Dr Green came to the camp :—

"The prisoners were spoken to on the subject, and seemed to be pleased with the idea, the word *tika* (inoculation), which was familiar to them from its association with small-pox, appearing to appeal to them. They were accordingly arranged in four rows facing the tent, in front of which Dr Haffkine was about to commence operations. I was the first subject to be inoculated; and after me the jailor, assistant jailor, hospital assistant, and three warders. The first prisoner in the front rank was next brought up and submitted cheerfully; after which, every alternate man was taken, so that no selection of cases was made, until one-half of the total number were inoculated. Those who had not been inoculated were far from pleased at having been passed over; and, to our surprise, they rose almost to a man, and begged to be inoculated; nor were they satisfied when told that the medicine was exhausted."

The dose administered on this occasion (11th April 1896), was stronger than the Gaya jail dose (18th July 1894): it acted in a few hours, and the reaction was well marked.

"There were fresh cases of cholera that day at 12 (noon), 6, 6, 7, and 7.30 P.M., and at midnight, all in those who had not been inoculated, and all terminating fatally, despite the greatest care and the most prompt and assiduous treatment. On the 12th two further cases occurred, both among the uninoculated, and both died; there being thus eight

cases in succession, all from the men who were not inoculated, and all proving fatal."

The inoculations were made at 7.30 A.M. Surgeon-Captain Brown had pain within half an hour, and fever in three hours, with temperature 104°, *but this was probably due to the fact that I was not able to rest.* The prisoners, of course, went to bed: they all reacted before 4 P.M., but did not have so much trouble over it. The last case was on the 15th. The outbreak was a bad type of cholera; out of 30 cases 24 died, some of them in 1½ to 4 hours. "To summarise the combined results of the camp and the jail, we find that of a daily average of 99 non-inoculated there were 11 cases, all fatal = 11.11 per cent.; of 110 inoculated there were 5 cases, with 3 deaths = 2.73 per cent."

6. *Bilaspur and Serampur.*

Here again the figures are small, but worth noting. In a coolie camp at Bilaspur (Central Provinces) 100 non-inoculated had 5 deaths, and 150 inoculated had 1 death. In Serampur, among the general population, 51 non-inoculated had 5 cases and 3 deaths, and 42 inoculated had 2 cases and 1 death.

7. *The Cachar Tea-Gardens* (1895).

This series of inoculations was begun in February 1895, for the protection of the coolies on various tea-estates. The results are excellent, and deal

with large numbers.* The latest report from Dr Arthur Powell, the Medical Officer, is quoted in Dr Simpson's 1896 report:—

At Kalain—

1079 not inoculated had 50 cases, with 30 deaths.
1250 inoculated—3 cases, with 2 deaths.†

At Kalaincherra—

685 not inoculated had 10 cases, with 7 deaths.
155 inoculated—no cases.

At Degubber—

254 not inoculated had 12 cases, with 10 deaths.
407 inoculated—5 cases, all recovered.

At Duna—

121 not inoculated had 4 cases, with 2 deaths.
29 inoculated—no cases.

At Sandura—

454 not inoculated had 2 cases, with 1 death.
51 inoculated—2 cases, with 1 death.

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* "As a field for testing the value of inoculation, the tea-factories of India possess many advantages. The labourers being under contract, the after-history of those inoculated is easily followed up. Each morning the adults are paraded for roll-call; and all sick must attend hospital, where a record is made of their disease and treatment." (Dr Powell, *Lancet*, 13th July 1896.)

† "It is unfortunate that neither of the fatal cases among the inoculated was seen by any medical man, not even an unqualified doctor Babu." Dr Powell does not think, from what was told him, that one of them was cholera.

At Karkuri—

198 not inoculated had 15 cases, with 9 deaths.
443 inoculated—3 cases, with 1 death.

At Craig Park—

185 not inoculated had 1 fatal case.
46 inoculated—no cases.

TOTAL.

Not inoculated, 2976, with 94 cases and 60 deaths.

Inoculated, 2381, with 13 cases and 4 deaths.

To the preceding instances, which are rather old now, must be added the following more recent report, from the *Indian Medical Gazette*, September 1901 :—

"We are glad to see, from a paragraph in the Report of the Sanitary Commissioner for Bengal (Major H. J. Dyson, I.M.S., F.R.C.S.), that an increased number of anti-cholera inoculations were performed during the year 1900. Assistant-Surgeon G. C. Mukerjee, who was in charge of this work, reports that in the Puralia Coolie Dépôt no less that 13,291 persons were inoculated against cholera, including over 1000 children. All these cases of inoculation were among labour emigrants proceeding to the tea-gardens of Assam and Cachar. The employers of labour are beginning to realise the value of cholera inoculation. It is unfortunately not always easy, or even possible, to follow up the after-history of persons inoculated; but Major Dyson has quoted a table, received from the

Superintendent of Emigration, which shows the number of cases among the inoculated and the non-inoculated at Goalundo. From this table, it is seen that out of 1527 non-inoculated coolies, who passed through Goalundo, 33, or 2.09 per cent., got cholera; whereas of 873 inoculated coolies, only 2, or 0.2 per cent., were attacked by the disease; that is, the unprotected suffered about ten times as much as the inoculated. Assistant-Surgeon Mukerjee also reports that during his cold-weather tour he passed through some villages in the Manbhum district, in which he had practised inoculation the previous year: and, though there had been epidemics of cholera in them, the inoculated persons escaped. They came to him in numbers, stating that they owed their safety to the inoculation."

Of course, the preventive treatment touches points only here and there on the map of India, with its 300,000,000 people. Probably it will never become so general in India as vaccination. Cholera in India recalls what Ambroise Paré, more than 400 years ago, wrote of the plague, "Here in Paris it is always with us." But, wherever preventive inoculation has been done, there it has done good.

Another most important result of the discovery of the cholera bacillus is its use in diagnosis. For example, if a case of suspected cholera is landed at a British port, the sanitary authority at once takes steps to ascertain whether the specific microbe is present; and, according to the answer given by bacteriology, either allows the patient to proceed on his journey, or adopts measures of isolation to pre-

vent the spread of the disease to others. Thus, thanks to the insular position of Great Britain, this dreadful disease has for many years been prevented from invading her population.

Men talk about Empire-building, and "Deeds that won the Empire," and they know nothing of the everlasting work that Haffkine and the doctors have done for the consolidation of India. Already, in 1896, he was working not at cholera only, but also at plague. Then, in January 1897, came the first anti-plague inoculations, and the outbreak of bubonic plague in the Byculla jail, Bombay.

VIII

PLAGUE

THE *bacillus pestis* was discovered by Kitasato and Yersin, working independently, in 1894. Yersin's discovery was made at Hong Kong, whither the French Government had sent him to study plague: an excellent account of his work is given in the *Annales de l'Institut Pasteur*, September 1894. The first experiments in preventive inoculation, in animals, were made by Yersin, Calmette, and Borrel, working conjointly, in 1895. They found that it was possible to confer on animals a certain degree of immunity, by the hypodermic injection of dead cultures of the bacillus. These experiments were made on rabbits and guinea-pigs.

Haffkine's fluid was first used on man in January 1897. It is a *bouillon* containing no living bacilli, and nothing offensive to the religious beliefs of India.* He proved its efficacy on rabbits; and

* It is said that the Jains object to inoculations on the grounds of religion; and one or two witnesses before the Plague Commission gave evidence to the same effect. But, at Bombay, the high-priest of a great religious community

then, on 10th January 1897, inoculated himself with a large dose, four times as strong as the subsequent standard dose. A few days later, Lieut.-Col. Hatch, Principal of the Grant Medical College, Bombay, and other members of the College Staff, were inoculated. These first inoculations were described by Haffkine in a recent lecture (1901) at Poona :—

"In a short time, a number of the most authoritative physicians in Bombay, European and native, official medical officers and private practitioners, submitted themselves for inoculation. It is a matter of gratification to me to be able to quote, among these authorities, the Head of the Medical Service of the Presidency, Surgeon-General Bainbridge, who not only got himself inoculated, but inoculated also the members of his family. Previous to that, Surgeon-General Harvey, the able Director-General of the Indian Medical Service, submitted himself to inoculation in 1893 against cholera; and, in 1898, against plague. It was the example of these gentlemen, whose competence in the matter of health could not be disputed, that encouraged thousands of people, rich and poor, in Bombay and elsewhere, to come forward for inoculation. Thus his Excellency the Viceroy thought it right to tell you here, in Poona, that previous to his starting for the plague-stricken districts he and his staff had also undergone the prophylactic inoculation. In due

addressed a meeting of 5000 in favour of the new treatment; and the rush of suppliants for inoculation at Hubli and Gaday proves that there is no real religious difficulty. Doctors have been assaulted, as at Poona, so at Oporto; in neither case can we say *Tantum relligio potuit suadere malorum.*

course, mothers brought their children to be protected by the new 'vaccination.'"

Within a few months, 8142 persons in or near Bombay were inoculated. It was not possible, in Bombay, during the rush of plague-work, to follow up every one of these 8142 persons. But there is reason to believe, making some allowance for oversights, that only 18 = 0.2 per cent. of them were attacked during the epidemic; that, of these 18, only 2 died: and that these 2 died within twenty-four hours of inoculation, *i.e.*, had the plague in them already at the time of inoculation.

And, with regard to a small group of the inoculated, there are the following more definite facts. This group lived outside Bombay, across the harbour, in a village called Mora. The population of Mora, at the time of the epidemic, was estimated at less than 1000. Out of this number 429 were inoculated; which, if the population be reckoned at 1000 exactly, left 571 uninoculated. Among the 429 inoculated, there were 7 cases of plague, with no deaths: among the uninoculated there were 26 cases, with 24 deaths.

Just a week after Haffkine had informed the Indian Government that he had tested his fluid on himself, plague broke out in the Byculla House of Correction, Bombay, on 23rd January 1897. Between the 23rd and the afternoon of the 30th, there were 14 cases, with 7 deaths. On the afternoon of the 30th, 152 prisoners were inoculated, and 172 were left uninoculated. The outbreak ceased on 7th February. The figures, as corrected

by the Plague Commission, are, among the inoculated, 1 case, which recovered; among the uninoculated, 7 cases, with 2 deaths.

For a full and severe examination of the reports, statistics, and other evidence concerning this and other outbreaks in which preventive inoculations were made, the Report (1901) of the Indian Plague Commission must be studied. The Commissioners, Professor T. R. Fraser, Mr J. P. Hewett, Professor A. E. Wright, Mr A. Cumine, Dr Ruffer, and Mr C. J. Hallifax, Secretary, travelled and took evidence in India from November 1898 to March 1899: during which time they held 70 sittings and examined 260 witnesses, some at great length. The evidence and the report are published in five large volumes. The report, 540 pages in all, deals exhaustively with the whole subject. It represents the very least—what might almost be called the very worst—that can be said of Haffkine's fluid: and, of course, it reads rather differently from the reports of the men who, with their lives in their hands, and worked almost past endurance, fought plague themselves. The following paragraphs give, so far as possible, the bare facts of various outbreaks of the disease in 1897-99, in which Haffkine's fluid was used.

1. *Daman.*

Plague broke out in Daman, a town in Portuguese territory, north of Bombay, and in constant communication with Bombay by sea, in March 1897. By the end of the month, when a Government

cordon was placed round the town, about 2000 out of 10,900 had fled. The outbreak reached its height in mid-April, and was practically over by the end of May. Inoculations were begun on 26th March. The total population on that day (2000 having gone out, and 670 having died of plague) is estimated at 8230. Of these, 2197 were inoculated, and 6033 were left uninoculated. Among the inoculated there were 36 deaths = 1.6 per cent.; among the uninoculated 1482 deaths = 24.6 per cent.

The Commissioners criticise these figures severely, and do not accept them as exact. But they admit the evidence as to the results of inoculation among the Parsee community of Daman. Of this community, 306 in number, 277 were inoculated, and only 29 were left uninoculated. Among the inoculated there was 1 death = 0.36 per cent.: among the uninoculated there were 4 deaths = 13.8 per cent.

They admit, also, the house-to-house investigations made by Major Lyons, I.M.S., President of the Bombay Government Plague Committee. At the end of May, he visited 89 houses, in 62 of which both inoculated and uninoculated were living together. He found that out of 382 inoculated, 36 had died = 9.4 per cent.; out of 123 uninoculated, 38 had died = 30.9 per cent.

2. *Lanauli.*

Plague attacked Lanauli, a small hill-station and railway dépôt, during April-September 1897. The entire population was estimated at about 2000.

Inoculations were begun on 24th July in two wards of the town, and a daily house-to-house inspection was instituted. The figures reported, on the basis of the average daily strength of the two groups, are as follows :—

Inoculated, 323, with 14 cases, of which 7 died = 2 per cent.

Uninoculated, 377, with 78 cases, of which 57 died = 15 per cent.

The Commissioners criticise the method on which these figures are based, and do not accept them as accurate. But they agree that inoculation "exerted a distinct preventive effect"; and they admit Major Baker's evidence—"In the place where inoculation had been made use of, the town was thriving and full of people; and the other part of the town was absolutely empty. One side had plague, and the other had none."

3. *Kirki.*

The figures here were obtained under especially favourable circumstances; and the Commissioners have, practically, no fault to find with their accuracy. The following account is by Surgeon-Major Bannerman, Superintendent of the Plague Research Laboratory, Bombay :—

"Plague broke out in Kirki, in the artillery cantonment, situated four miles from Poona; and the followers of the four batteries stationed there suffered severely. These men were living with their families in lines on a sloping plain, under

military discipline, and in circumstances far superior in a sanitary sense to those of the average villager. When the disease appeared, the lines were isolated, so that none could enter or leave without the knowledge of the military. A special hospital was erected close by, where all sick persons were sent as they were discovered by the search parties of European artillerymen, who visited each house thrice daily. It is therefore probable that all cases of plague were promptly discovered and removed to hospital: and in each case the usual disinfection was thoroughly and systematically carried out. Yet, in spite of all this, it was found that, in those not protected by inoculation, 1 out of every 6 of the population was attacked, and 2 out of every 3 attacked died. The epidemic was, therefore, a severe one. The population of the lines numbered 1530; and, out of these, 671 volunteered for inoculation. At the close of the epidemic, the plague-hospital admission and discharge book was examined, and compared with the register of those inoculated, when the following result was got. The population operated on being under military discipline, and confined to their lines, makes the accuracy of the figures undoubted:—

Inoculated, 671, with 32 cases, of which 17 died = 2.5 per cent.
Uninoculated, 859, with 143 cases, of which 98 died = 11.4 per cent.

"Here, then, is seen a body of people divided into two groups by the fact that one had undergone inoculation and the other not, *but differing in no other way*, reacting towards plague in such a markedly different manner that the conclusion is

forced on one, that the inoculation must be the cause. Seeing the absolute similarity of conditions, *the* 671 *inoculated should have had proportionately* 112 *cases and* 77 *deaths, if they had remained as susceptible to the disease as their uninoculated brothers, sisters, parents, wives, husbands, children; but, instead of that, they had only* 32 *cases and* 17 *deaths.* This death-rate would doubtless have been still further reduced, but for the fact that a very much weakened vaccine had to be used, owing to the demand having got beyond the resources of the laboratory at that time."

4. *Belgaum.*

In Belgaum, a town of Southern India with a normal population of about 30,700, two outbreaks of plague occurred in quick succession. The first outbreak lasted from November 1897 to May 1898; the second, from July 1898 to January 1899. During the two epidemics, 2466 persons were inoculated. Of these, it was reported that only 61 (or 62) had been attacked, of whom 33 died = 1.34 per cent. But these figures, in the judgment of the Commission, cannot be accepted as even approximately correct. There are, however, two groups of these Belgaum cases, one of which the Commission admits as substantially accurate, and the other as absolutely accurate. These groups are, (1) the Army cases; (2) the cases reported by Major Forman, R.A.M.C., Senior Medical Officer of the Station.

(1) *The Army cases.*—These cases occurred in the 26th Madras Infantry, which was living in lines

close to the cantonment and the city. The first case of plague in the regiment was on 12th November 1897. Ten days later, the regiment was moved out into camp. Inoculation was begun, by Surgeon-Major Bannerman, on 23rd December, up to which time there had been, among the regiment and its families and followers, 78 cases, with 49 deaths. The following account of the inoculations is given by Surgeon-Major Bannerman :—

"No difficulty was experienced in persuading the men to consent to inoculation, when it was explained to them that they would be free to return to their houses in the lines after being operated on. General Rolland was the first to be operated on, and his example, combined with that of the officer commanding, and their medical officer, who were all operated on in front of the men, sufficed to convince the Sepoys of the harmlessness of the operation: and the only difficulty that then remained was to perform the operation fast enough. . . . The community was, practically, completely inoculated by the end of the year. The total operated on was 1665, out of a population of 1746 living in the lines at that date. The 81 not operated on were infants, women far advanced in pregnancy, and the sick in hospital chiefly, though one solitary Sepoy has, up to the present time, refused to submit to operation."

From this time onward to the end of the first epidemic, though the disease was at its height in January in the neighbouring city and cantonment, and though the men were allowed to go freely to

these places after inoculation, *only 2 out of the 1665 were attacked, and both recovered.*

When the second epidemic came, in July 1898, the troops, families, and followers, were reinoculated at their own request, 1801 in all. "Practically no one was left in the lines unprotected by inoculation." From this time onward to the end of the second epidemic, though it was much more severe than the first, only 12 cases occurred. *In the first epidemic, before inoculation, 78 cases occurred, and 2 after it: in the second, and much more severe, epidemic, though the sanitary measures adopted in both epidemics were similar, only 12 cases occurred.* "It would hardly appear to be open to doubt," says the Commission, "that the practical immunity of the regiment, during the second outbreak, was due to inoculation."

(2) Major Forman's evidence before the Commission is very striking, though the figures are small. The following abstract of it is given in the Report of the Commission :—

"The groups of persons, concerning whom Major Forman gave us evidence, were his private servants, and the hospital attendants of the Belgaum Station Hospital with their wives and children. He inoculated these groups when plague first broke out in the town, and was able to keep in touch with them continuously after that time. Regarding the first group, he says, bringing down their history to 3rd March 1899, 'Of my private servants there were in all, including their wives and children, 28 people inoculated. There have been no cases of plague, and no deaths up to date. There were 3 uninoculated. One was a child of 9 years of age,

whose father refused to allow it to be inoculated. It died of plague 12 days after the other people were inoculated. The other 2 cases that were not inoculated were not so distinctly under my own observation. One was a sweeper employed in the cantonment, and sleeping in my compound: he, I am told, died of plague some months afterwards. The other was my water-carrier: he threw himself into a well: I was informed that he had buboes and fever, and ran away to escape segregation. Of the 28 inoculated, none died of plague: and of 3 uninoculated, 2 are said to have died of plague, and 1 undoubtedly died of plague.'"

"Regarding the second group of which he gave us particulars, Major Forman said that, out of 90 hospital servants, 87 were inoculated. Of the inoculated persons, 1 died from fever and endocarditis, and 1 died of plague. Excepting these two, the rest of the inoculated were alive and well in March 1899. Only 3 persons remained uninoculated. Of these, one was not operated upon, because she had recently been delivered; another was not operated upon, because she was pregnant; and the third was a boy of 16 years of age, whose father refused to let him be inoculated. The boy died of plague, two months after the inoculation of the rest of the hospital servants had been done. One of the two uninoculated women died of plague two days after the boy, she having been in attendance upon him. The other uninoculated woman remained well."

5. *The Umarkhadi Jail, Bombay.*

Plague broke out in this jail on the last day of 1897, and 3 prisoners died. Next day, 1st January

1898, all the prisoners were paraded, and all were willing to be inoculated. But it was decided to divide them into two equal groups, and inoculate one group. There were 402 altogether: 2, when their turn came, refused to be inoculated: thus 199 were inoculated, and 203 were left uninoculated. No distinction was made between the two groups: "They had the same food and drink, the same hours of work and rest, and the same accommodation." The plague did not come wholly to an end till March. The figures, since the inmates of a jail are a shifting population, are based on the average daily number of each group: this was 147 for the inoculated, and 127 for the uninoculated. The figures are:—

Average Daily Number.		Cases.	Deaths.
Inoculated .	147 .	3	0
Uninoculated .	127 .	9	5

The Commission draw attention to "the important fact that, during the whole period of the outbreak, the number of attacks among the inoculated was only one-third of the number among the uninoculated; and that the disease among the inoculated was remarkably mild resembling mumps more than plague, though the cases among the uninoculated were of average severity." According to Surgeon-Major Bannerman, the hospital authorities were doubtful whether these three cases among the inoculated were plague at all.

6. *Undhera.*

The figures for Undhera are very valuable: "The conditions," says Surgeon-Major Bannerman, "approached very nearly the strictness of a laboratory experiment." Even the Commissioners are enthusiastic here.

Undhera is an agricultural village, 6 miles from Baroda. Plague broke out in it, in January 1898. A careful census was taken, and showed a population of 1029. By 12th February there had been 76 deaths. On that day the village was visited by Mr Haffkine, Surgeon-Major Bannerman, and other experts, and 513 persons were inoculated:— *By reference to the census papers, the whole of the inhabitants were called out, house by house, and the half of each household inoculated. In this way, an endeavour was made to inoculate half the men, half the women, and half the children in each family, and to arrange that a fairly equal proportion of the sickly-looking should be placed in each division.* The plague lasted 42 days after the inoculations, and affected 28 families. On 4th April a house-to-house investigation was made by Mr Haffkine, Surgeon-General Harvey, Surgeon-Major Bannerman, and Captain Dyson. The figures are as follows:—

Population on 12th February.		Cases.	Deaths.	Mortality.
1029−76=953	Inoculated, 513	8	3	0.6 per cent.
	Uninoculated, 440	28	27	6.0 per cent.

Thus, out of 28 families, where the protected and the unprotected lived and ate and slept together, the protected, 71, had 3 deaths; and the unprotected, 64, had 27. The percentage of attacks was four times higher among the unprotected; the percentage of deaths was ten times higher.

7. *Khoja Community, Bombay.*

The head of this community, H.H. Sir Sultan Shah, Aga Khan, K.C.I.E., opened a private station for the inoculation of the community in March 1897, and again in December of that year. He was himself inoculated three times, and many of the community so often as five times. The work of inoculation went on daily, and by 20th April 1898 the number of persons inoculated or reinoculated was 5184. The whole community, according to a careful census taken at the beginning of 1898, numbered 9350; but, since many families had fled to avoid the infection, this number is too low. The Commissioners guess 9770: Haffkine, to the disadvantage of his own statistics, guesses so high as 13,330. The number of the inoculated or reinoculated shifted, of course, as the work went on: their average daily number during the four months of plague, January to April 1898, was 3814.

During these four months, the number of deaths *from all causes* in the whole community was 184. According to the average mortality of the community in times of no plague, the deaths *from all causes* during four months would be 102. It may

fairly be assumed that the extra deaths, 82, were due to plague: and, indeed, 64 plague-deaths were either acknowledged by the relatives, or certified by the burial-books of the community. *Of these 82 deaths, 3 occurred among the inoculated or reinoculated, and 77 among the uninoculated.*

The Commissioners find fault with these figures: "Nevertheless, quite apart from the statistics put before us, which we think inaccurate, we do not doubt that inoculations had a good effect, especially as much weight must be allowed to the opinion of a community so intelligent as that of the Khojas."

8. *Hubli.*

This, the greatest and most amazing of all instances of preventive plague-work, was done in a town of 50,000 persons. The following report, by Surgeon-Captain Leumann, was forwarded to the Plague Commissioners by Mr E. K. Cappel, Collector of Dhárwár, with this comment:—

"The town of Hubli—a mercantile town of over 50,000 inhabitants—was attacked by plague in an epidemic form at the commencement of the monsoon rains. The average rainfall between April and October amounts to more than 28 inches. Under these circumstances, although a large and weather-proof health camp had been prepared for emergencies, complete evacuation of the infected town-site was impossible; and the attempt to effect it would have led to the severest hardships and to the immediate spread of the disease into surrounding villages and districts. It was for this reason that

the determination was formed to make a bold and comprehensive experiment with the prophylactic, and not on any *à priori* grounds. If this experiment had failed, the results, judged by the actual mortality among the uninoculated, would have been appalling. *All possible sanitary measures in the shape of disinfection, unroofing of houses, and segregation, were applied concurrently with inoculation, as Government are already aware; but the rate of mortality among those who held back from inoculation rose at one time to a height which, I believe, has never been approached elsewhere. . . .*

"However, the experiment, in the hands of Dr Leumann, did not fail, and it has afforded a demonstration of success which is of Imperial importance. Many thousands of lives have undoubtedly been saved, and at the present moment the plague mortality is merely sporadic, and Hubli is steadily regaining its normal population and trade, though surrounded by infected villages."

The Hubli report must be put at full length, for the vivid picture it gives of plague in India, and of the difficulties besetting the magnificent work of the Indian Medical Service. It is a story that Mr Kipling ought to write. And it is to be noted that Surgeon-Captain Leumann, who saved Hubli, recognised the extreme importance of other methods than inoculation — disinfection, isolation of cases, evacuation of infected districts. He says:—

"While paying the highest tribute to the value of Mr Haffkine's inoculation method, which I claim, here in Hubli, to have put to perhaps the severest test to which it has yet been subjected, I am of

the opinion that individual protection is, on however great a scale conducted, of less importance to that of general protection and hygiene (considering each method separately, that is to say), for it seems to me more radical, if not more rational, to eradicate a disease than to leave it to pursue its course and only protect people against its ravages."

Sanitation, therefore, was Dr Leumann's faith. Now for his works :—

"I first started inoculation here on 11th May. . . . When I began my inoculations, I operated first of all on some European or native gentlemen in front of a crowd of poor and low-caste people, whom I had gathered together in the worst-affected area, and they were thus soon induced to ask for inoculation themselves. . . . They have presented themselves, by the hundred, at all times of the day, before myself and others, for the purpose of being inoculated.* . . . I have never experienced the slightest difficulty in inoculating Mussulmanis or any other purdáh women in Hubli. . . . The very men who, in March last, created a disturbance in Hubli, were not only the first and the most willing to undergo inoculation, but also to bring their wives and families to my hospital, or to invite me to their homes to inoculate them.

"Inoculated persons holding certificates of double inoculation have, at my special wish and order, been

* Compare the account of the inoculations at Gaday, in the *Lancet*, 11th February 1898 : "To see the crowd waiting and struggling to pass the barrier is a strange sight ; old men and women, young children, and mothers with babes in their arms, form a daily crowd numbered by hundreds, who wait for hours to get their chance of the day's inoculation."

left in their homes throughout this epidemic; only their clothes, house, and property being disinfected on the occurrence of a plague case or death in their house. As the vast majority of plague cases have never been notified before death in Hubli (nor, in my experience of nearly two years, elsewhere, if native supervision be largely resorted to), it will readily be understood that the majority of the inoculated have actually been living in the same house, or even room, with a plague case (often of the pneumonic type, whose terrible power of spreading the disease was first shown by Professor Childe, I.M.S., of Bombay) during the whole of the time that case was living, probably attending on the patient, breathing the same stuffy air, and, perhaps, sharing the same blanket; and I attach at the end of this report a long series of cases where such conditions have occurred, *the non-inoculated dying of plague, and the inoculated escaping, almost to a man.*

"Various critics on my work, not knowing what the actual facts were and are, have at different times asserted that the inoculated inhabitants of Hubli left the town in larger numbers than the non-inoculated. Exactly the reverse was the case. The British officers on plague duty here, and all the Divisional Superintendents, invariably replied (officially and in writing when so required) that the non-inoculated left Hubli in far greater numbers and proportion than the inoculated; and my own observations entirely bear out this statement.

"It has been urged that those who received inoculation were of a class or classes better protected than others against plague by reason of their habits, the food they eat, the houses they live in, etc. In reply, I unhesitatingly state that if there be but one town in India where that line

of argument will not hold good, it certainly is Hubli; for *not only were the poorer, dirtier, lower-caste people the first to be persuaded to receive inoculation, but I made it my personal and special duty to work amongst them.* My first few thousand inoculations were almost entirely amongst the lowest and poorest of the people. The Brahmins are, perhaps, of all castes, supposed to be the most cleanly in their houses, habits, etc., yet the Brahmins of Hubli (who at first, imagining themselves immune, were the foremost and greatest perverters of the truth concerning its efficacy, and the last to apply for the protection inoculation affords), simply inundated the various inoculation centres, as soon as plague began to spread in their midst, clamouring for the very method of which they had only lately tried to prevent others from availing themselves.

"Unfortunately, the average native, educated or not, appears to have the very greatest aversion to notifying any case of sickness—plague or other—and hence, in my opinion, it becomes more necessary than ever to protect the people by inoculation, since they will not help to protect themselves by the foremost and simplest of sanitary and hygenic measures.* With so few police (and

* Compare the account given by the Rev. H. Haigh (*Methodist Recorder*, December 1898), of the plague at Bangalore: "The native population do all they can to elude the vigilance of the authorities. In order to escape segregation, the householders in many instances refrain from reporting plague, and not infrequently bury the corpse secretly. Not only is any spare piece of ground used as a burial-place, but the body is at times thrown into a well or tank, or dropped over the wall of some European compound. During one week three plague corpses were found, badly decomposed, in reservoirs commonly resorted to for drinking purposes."

those none too good) to help one; an inadequate British Staff; with so much reliance placed in Native Superintendents and Supervisors, and a Municipality so bankrupt that it could not apparently afford to buy enough blankets out of its own funds for the patients in the Plague Hospitals — the work of segregation, house-to-house inspection, etc., became, from a medical point of view, absurdly insufficient.

"The total number of inoculations performed in Hubli, both on actual inhabitants and on people from outside (villages) between 11th May and 27th September, amounts to some 78,000 altogether."

I.

Dates.	Census of Hubli.	Non-inoculated.	Inoculated.	Plague-deaths among Non-inoculated.	Plague-deaths among Inoculated.
Five weeks from May 11 to June 14	Fell from 50,000 to 47,427	44,573	2,854	47	1
Week ending June 21	47,082	41,494	5,588	22	3
„ June 28	47,485	39,042	8,443	29	1
„ July 5	46,537	36,020	10,517	55	6
„ July 12	46,518	33,255	13,263	34	6
„ July 19	45,240	29,716	15,524	82	7
„ July 26	43,809	24,112	19,697	100	15
„ Aug. 2	43,707	21,031	22,676	140	16
„ Aug. 9	42,768	15,584	27,184	272	19
„ Aug. 16	40,441	10,685	29,756	386	61
„ Aug. 23	39,400	6,367	33,033	371	41
„ Aug. 30	38,210	4,094	34,116	328	28
„ Sept. 6	38,382	2,731	35,469	227	34
„ Sept. 13	38,408	1,116	37,292	138	47
„ Sept. 20	39,142	937	38,205	106	55
„ Sept. 27	39,315	603	38,712	58	20

II.

Dates.	Plague death-rate. Comparison per 1000 between		Percentage reduction of Plague death-rate in favour of the Inoculated.
	Non-inoculated.	Inoculated.	
Five weeks from May 11 to June 14	1.022	.350	Over 65 per cent.
Week ending June 21	.530	.527	About 1 „
„ June 28	.742	.118	Nearly 85 „
„ July 5	1.524	.570	About 63 „
„ July 12	1.022	.452	Nearly 56 „
„ July 19	2.793	.450	84 „
„ July 26	4.147	.761	82 „
„ Aug. 2	6.656	.705	89 „
„ Aug. 9	17.325	.698	Over 96 „
„ Aug. 16	33.694	2.083	94 „
„ Aug. 23	57.011	1.241	98 „
„ Aug. 30	80.116	.820	98 „
„ Sept. 6	83.112	.958	99 „
„ Sept. 13	112.903	1.260	Over 99 „
„ Sept. 20	113.127	1.439	Over 99 „
„ Sept. 27	96.185	.517	Over 99 „

"It appears that if the 47,427 inhabitants had remained, as they did—in their town, without running away by rail or otherwise, or without camping out in a mass—and if no inoculation had been resorted to—they would have lost 24,899 souls, or a little over a half of their number. The official records show that this has actually occurred, during the present terrible outbreak, in a number of large villages, of 2000 inhabitants and over, in the Hubli *taluka* and elsewhere in the Dhárwár District, where no inoculation was done, and no camping-out was possible on account of the wet weather." (Haffkine's commentary on Dr Leumann's report.)

That is the story of Hubli; and, as it stands, it is almost incredible. The Commissioners, by very strict inquiry, reduced it to credibility without robbing it of glory. The inquiry brought out more instances of the immeasurable difficulty of

the work. Natives who wished to avoid inoculation would escape through the back door at the sight of a plague officer: bribery, personation, sale or transfer of certificates of inoculation, concealment of cases and of deaths, were all practised by those who wished not to be inoculated, or to get the privileges of the inoculated without inoculation, or to save their infected houses from being disinfected and unroofed. Again, with the people dying like flies, and many of them bearing no mark of identification, and with the medical officers overworked past human endurance, the wonder is, not that the statistics were faulty, but that there are any statistics at all. Certainly, the Commission is well within the mark in saying, "It is quite clear that a very large number of lives must have been saved in Hubli by inoculations during the whole course of the epidemic there. *Moreover, we may note that an arithmetical estimate is not the only criterion by which we can appreciate the value of inoculations. And in Hubli their value is approved by the consensus of opinions of officers who have seen probably far more of this process and its results in practice than any other persons in India, and who, having every facility for forming a sound judgment as to its effect where plague was really virulent, are satisfied as to its great value.*"

Finally, as at Daman so at Hubli, there are lesser groups of statistics, of that kind which is *approved by the consensus of opinions of officers.* These are, (1) Lieutenant Keelan's house-to-house investigation; (2) the Southern Mahratta Spin-

ning Mills; (3) the Southern Mahratta Railway employés.

1. Lieutenant Keelan made a house-to-house visitation of 200 houses, in each of which there were protected and unprotected persons living together, and in each of which there had been one or more cases of plague. The figures for 69 of these houses are appended to Captain Leumann's report. They are as follows:—

	Inmates.	Cases.	Deaths.	Mortality.
Inoculated .	336	11	4	1.19
Uninoculated.	144	84	80	55

These 69 houses were selected: there was nothing unfair in the method of selection, still, they were "good houses"; they are not, therefore, exact for statistics; but, as the Commissioners say, they are "of interest as quite special examples of successful inoculation."

2. In the Southern Mahratta Spinning and Weaving Company's Mills, a careful record of inoculation was kept and checked by the manager. The number of the workpeople at the time when inoculation was begun, 21st June, was 1173. At the end of the epidemic the figures were:—

		Deaths.	Mortality per cent.
Inoculated twice .	1040	22	2.11
Inoculated once .	58	8	13.79
Uninoculated .	75	20	26.66

Here, again, the figures have not a statistical value: "We are not informed whether the inoculations were performed simultaneously; or at what stage of the outbreak the average strength of the inoculated was reached." All the same, what Major Bannerman says of them is true—*The experience in this company's mill at Hubli should be an object lesson to all mill-owners in plague-stricken towns.*

3. The figures for the Southern Mahratta Railway are given by Major Bannerman in his "Statistics" (1900): they are not mentioned in the Report of the Plague Commission. They are of great value, because the daily shifting of the numbers was recorded as the work of inoculation went on, and the date of each case of plague was also noted. Major Bannerman gives the following account:—

"The railway employés were living in barracks, and in the railway yard, apart from the general population of Hubli town. *They were under close daily inspection by English officials,* who formed a committee for this purpose, with Dr Chenai as their medical adviser. The results may therefore be regarded as accurate in a high degree, the numbers dealt with not being excessive, and the supervision strict."

The figures, based on the average numbers in each group, are as follows:—

	Cases.	Deaths.	Mortality per cent.
Twice inoculated . 990	6	1	0.1
Once inoculated . 270	5	1	0.3
Uninoculated . 760	35	21	2.7

These eight instances must suffice: many must be left out—among them, Dhárwár and Gadag, where Miss Corthorn, M.B., did work as splendid as Leumann's work at Hubli; and Mr Anderson's work in the Ahmednagar villages; and many more. These plague-reports are to be read, not for their record of heroic zeal and resourcefulness, but only as one more example of many thousand lives saved by a method learned from experiments on animals.

But, of course, there is not, and perhaps there never will be, a national acceptance and adoption of this method through the length and breadth of India. It does not work miracles; it is an uncomfortable process to submit to; privileges must be offered with it, or the native will often prefer to take his chance; the protection is of uncertain duration; all sorts of lies are told about it, partly by anti-vivisectionist writers, partly by native political agitators, partly by the *hakims*. For instance, at a meeting of *hakims* at Masti, Lahore, on 11th April 1898, the following resolutions were passed:—

"That in the opinion of this meeting the bubonic plague is not a contagious disease. It originates from poisoned air, and this poison is created in the air on account of atmospherical germs and the excess of terrestrial humidities.

"That this meeting, having carefully considered the Resolution of the Punjab Government (11th January 1898), is of opinion that the rules embodied in that Resolution (isolation, disinfection, etc.), are

unnecessary under the principles of Unani medical science."

And among statements to be made to the Plague Commissioners was the following, from a native practitioner in Bombay (April 1899):—

"I do not think the plague was imported in Bombay from Hong Kong or anywhere else. I attribute three sources of causes of outbreaks of plague in Bombay: (*a*) The predisposing cause was the Bombay Municipality; (*b*) The exciting cause was the Nature herself; (*c*) The aggravating cause was the Plague Committee."

All these difficulties were well stated by Surgeon-General Harvey, Director-General of the Indian Medical Service, at the discussion on Haffkine's discourse before the Royal Society, June 1899:—

"The people of England should consider the difficulties attending the work of a bacteriologist in India. . . . He had no doubt as to the value of the inoculations. At Undhera he carefully examined the results of the experiment, and, as far as he could judge, there was no possibility of error. The results in that experiment were such as to be 90 per cent. in favour of the inoculated against the uninoculated. The natives of India were, however, a strange people, and it was difficult to prophesy how they would act. In Calcutta, the mention of inoculations had driven in hot haste from the city 300,000 people, many of whom afterwards returned and were inoculated; while at Hubli he had seen the inhabitants come in their thousands to be inoculated and pay for the inoculations. The medical

officer in charge at Hubli had performed about 80,000 inoculations, and had only observed some 12 abscesses. He thought that 12 abscesses only, in 80,000 inoculations, showed good results. But, after all, what were the numbers of inoculations performed to the 300,000,000 inhabitants of India? He felt that even if every one consented to be inoculated it was impossible to provide the vaccine or the medical officers for such a demand. It was accordingly to sanitary improvements that he looked with the most confidence to protect India against the plague."

Therefore, now and for many years to come, preventive inoculation must fall into line with the other world-wide ways of fighting plague—quarantine, notification, isolation, all sanitary measures, destruction of rats—*le rat, le génie de la peste*—evacuation of infected towns, disinfection or unroofing of infected houses. Happily, this is just what it does. That admirable paper, the *Indian Medical Gazette* (September 1901), has put this fact very simply: "No one ever imagined that inoculation was the *only* means of fighting plague. Its great value consists in its immediate application. To sanitate, ventilate, and practically rebuild a town or village takes time; and in the meantime thousands die." For sudden outbursts of plague—since rats are one chief source of infection, and notification is fundamentally abhorrent to native custom, and evacuation may ruin trade, or spread infection, or be impossible by reason of the rains—since "East is East, and West is West"—it is not always possible to provide, for an Indian village smitten

by plague, the excellent arrangements of the Western world. In all such cases, and in all cases of epidemic plague within narrow limits, as in jails, barracks, mills, and the like centres of human life; and in all inner communities, such as the Parsee community at Daman, or the Jewish community at Aden—by every test of this kind, the saving power of preventive inoculation has been proved, again and again, past all doubt. As for those larger death-traps, Hubli, Dhárwár, and the rest of them, here, though the statistics are inexact, we have the word of the men and women themselves who stood between the dead and the living, and the plague was stayed. Such faults as there were, in 1899, in the treatment—the contamination of this or that stock of the fluid, and the inadequate method of standardisation—have been duly noted by the Commission. The rush for the fluid in 1899 may be estimated from the following paragraphs:—

i. *Paris.* "The preparation of anti-plague serum is being rapidly proceeded with; up to the present time the Institute has supplied it, in response to all the very numerous requests which have come from Portugal, Spain, Italy, and Turkey, without encroaching on the reserve kept in readiness for Paris and the departments." (*Lancet*, 16th September 1899.)

ii. *India.* "The spread of plague westward to Spain and Portugal seems to have excited more or less general alarm, and I hear that an unprecedented demand has suddenly arisen for the plague prophylactic fluid. The Government of India have been

asked the cost of supplying from 50,000 to 100,000 doses, and the earliest date at which this quantity could be dispatched. It is also desired to know if in case of need 50,000 doses a week could be sent to London. Russia desires to obtain a considerable stock for Port Arthur. Italy has been making inquiries for home use; and also Portugal, in order to inoculate at Mozambique. The present laboratory is at Government House, Parel, Bombay, and has only recently been fitted up by the Government of India. About 10,000 doses a day can be turned out, but it is thought that still further enlargements will be required if the demand should increase beyond this amount." (*Lancet*, 23rd September 1899.)

It would take too long for the present purpose to consider what has been done, not only for the prevention of plague, but also for its cure by a serum treatment. The results obtained by this treatment in India have not been very good; but Yersin and others report better results in other countries. Good results are reported from Amoy (1896), Nhatrang (1898), Oporto (1899) and Buenos Ayres (1899-1900). In Glasgow, the prophylactic use of Yersin's serum seems to have done excellent service: the success of its curative use was not very striking. The curative results at Nhatrang (Yersin, *Annales de l'Institut Pasteur*, March 1899), are notable. Nhatrang is an Annamese fishing-village; and the plague, when it was left to itself, killed every case that it got:—

"La peste s'est montrée excessivement meur-

trière chez les Annamites. Sur 72 cas de peste, 39 personnes chez lesquelles la maladie a évolúe normalement, ou qui n'ont été traités que par des médecins indigènes, sont mortes sans exception. Les 33 autres cas ont pu être traités par le sérum, quelquefois dans de bonnes conditions, mais le plus souvent quelques heures seulement avant la mort. Malgré cela, nous avons obtenu 19 guérisons et 14 décès, ce qui fait une mortalité de 42 per cent., chez les traités. *Ainsi, d'une part,* 100 *pour* 100 *de mortalité chez les non-traités; de l'autre,* 42 *per cent. chez les malades qui ont reçu du sérum.* Ces chiffres confirment les résultats que j'avais obtenu en Chine en 1896."

A long review of this curative treatment, fairly hopeful but nothing more, is given in the Report of the Plague Commission, vol. v., pp. 269-320. The Commissioners are of opinion that it ought not yet to be extended, as a general measure, over all the districts affected with plague; and that there is need of more work in bacteriology before it can be thus extended. "We desire to record our opinion that, though the method of serum-therapy, as applied to plague, has not been crowned with a therapeutic success in any way comparable to that obtained by the application of the serum method to the treatment of diphtheria, *none the less the method of serum-therapy is in plague, as in other infectious diseases, the only method which holds forth a prospect of ultimate success.*"

IX

TYPHOID FEVER. MALTA FEVER

TYPHOID FEVER

THE names of Klebs, Eberth, and Koch, are associated with the discovery, in 1880-81, of the bacillus of enteric fever, *bacillus typhosus;* and it was obtained in pure culture by Gaffky in 1884. It has been studied from every point of view, in man and in animals; in the blood, tissues, and excretions; in earth, air, water, milk, and food; in its distribution, methods of growth, and chemical products. Especially, the study of its chemical products has been directed toward (1) immunisation against the disease, (2) bacteriological diagnosis of the disease at an early stage.

The date of the first protective inoculations against typhoid is July–August 1896: they were made at Netley Hospital, by Professor Wright and Surgeon-Major Semple. The first inoculations in Germany, made by Pfeiffer and Kolle, were published two months later. The story of these famous Netley inoculations is told in the *British Medical*

Journal, 30th January 1897. Eighteen men offered themselves—

"A good deal of fever was developed in all cases, and sleep was a good deal disturbed. These constitutional symptoms had to a great extent passed away by the morning, and laboratory work went on without interruption. . . . With two exceptions, all these vaccinations were performed upon Medical Officers of the Army or Indian Medical Services, or upon Surgeons on Probation who were preparing to enter those services."

Good luck attend all eighteen of them, and immunity against typhoid, wherever they are. The doses that they received were estimated in proportion to the dose that would kill a guinea-pig of 350-400 grammes weight; and the protective fluid contained no living bacilli:—

"The advantages which are associated with the use of such 'dead vaccines' are, first, that there is absolutely no risk of producing actual typhoid fever by our inoculations; secondly, that the vaccines may be handled and distributed through the post without incurring any risk of disseminating the germs of the disease; thirdly, that dead vaccines are probably less subject to undergo alterations in their strength than living vaccines."

The first use of the vaccine during an outbreak of typhoid was in October 1897, at the Kent County Lunatic Asylum. The treatment was

offered to any of the working staff who desired it :—

"All the medical staff, and a number of attendants, accepted the offer. *Not one of those vaccinated —84 in number—contracted typhoid fever: while of those unvaccinated and living under similar conditions, 16 were attacked.* This is a significant fact, though it should in fairness be stated that the water was boiled after a certain date, and other precautions were taken, so that the vaccination cannot be said to be altogether responsible for the immunity. Still, the figures are striking." (*Lancet*, 19th March 1898; see also Dr Tew's paper, in *Public Health*, April 1898.)

Certainly, they are striking; so is the story of the eight young subalterns on the Khartoum expedition, of whom six were vaccinated, and two took their chance. The six escaped typhoid, the two were attacked by it, and one died. But these figures are too small to be of much value.

The first anti-typhoid inoculations on a large scale were made among British troops in India (Bangalore, Rawal Pindi, Lucknow), when the Plague Commission, of which Professor Wright was a member, was in India, November 1898 to March 1899. These inoculations were voluntary, at private cost, and without official sanction; though the original proposal for them, in 1897, had come from the Indian Government. Pending official sanction, they were stopped. Then, on 25th May 1899, the Indian Government made application to the Secretary of State for India that they should be

sanctioned, and should be made at the public cost. The application is as follows:—

"The annual admissions *per mille* for enteric fever amongst British troops in India have risen from 18.5 in 1890 to 32.4 in 1897, while the death-rate has increased from 4.01 to 9.01; and we are of opinion that every practicable means should be tried to guard against the ravages made by this disease. The anti-typhoid inoculations have been, we believe, on a sufficiently large scale to show the actual value of the treatment, while the results appear to afford satisfactory proof that the inoculations, when properly carried out, afford an immunity equal to or greater than that obtained by a person who has undergone an attack of the disease; further, the operation is one which does not cause any risk to health. In these circumstances, we are very strongly of opinion that a more extended trial should be made of the treatment; and we trust that your Lordship will permit us to approve the inoculation, at the public expense, of all British officers and soldiers who may voluntarily submit themselves to the operation."

On 1st August, the Secretary of State for India announced in Parliament that this treatment, at the public expense, has been sanctioned.

On 20th January 1900, Professor Wright published in the *British Medical Journal* an account of these 1898-99 inoculations in India. "They were undertaken under conditions which were very far from ideal. In particular, there is reason to suppose that the results obtained may have been unfavourably influenced by a weakening of the

vaccine, brought about by repeated re-sterilisation." In no case was reinoculation done. The statistics were compiled from information furnished by officers of the Royal Army Medical Corps actually in charge of troops in the various stations; and were supplemented by reports received from the commanding officers of the various inoculated regiments. They are as follows:—

Numbers under Observation.	Cases.	Deaths.	Percentage of Cases.	Percentage of Deaths.
Inoculated . 2835	27	5	0.95	0.2
Uninoculated 8460	213	23	2.5	0.34

If the inoculated had been attacked equally with the uninoculated throughout the period of observation, they would have had 71 cases instead of 27.

These inoculations belong to the early part of 1899. During the rest of the year, inoculations were made in India, Egypt, and Malta: the results are given in an appendix to the Report of the Royal Army Medical Department, 1899. (See *British Medical Journal*, 21st September 1901.) The great majority of the troops tabulated were in India. Of the troops stationed at Malta, 61 were inoculated, 2456 not inoculated: among the former there were no cases, among the latter there were 17 cases and 5 deaths. In Egypt, of 4835 troops, 461 were inoculated; among these there were no cases, among the uninoculated there were 30 cases and 7 deaths. In India, of 30,353 troops, 4502 were

inoculated, leaving 25,851 not inoculated; among the inoculated there were 44 cases and 9 deaths, among the non-inoculated 657 cases and 146 deaths. Taking the Indian statistics, and estimating percentage to strength, we find, amongst the inoculated, admissions 0.98, deaths 0.2; amongst the non-inoculated, admissions 2.5, deaths 0.56. The cases which occurred amongst the inoculated men were in the majority of instances of a mild character. Taking Malta, Egypt, and India together, it appears that the inoculated, if they had suffered equally with the non-inoculated, would have had 108 cases and 24 deaths, instead of 44 cases and 9 deaths.

At the end of 1899, this treatment, only just out of the hands of science, was suddenly demanded for the protection of a huge army at war in a country saturated with typhoid. Still, the South African results, and other results during 1899 to 1901, show a good balance of lives saved. The following paragraphs give all results published up to the present time, from the beginning of 1900 to May 1902. They are put in order of publication. Doubtless a few other reports have been overlooked in compilation; but the list includes all that were easily accessible.

1. *Manchester, England.* The *British Medical Journal*, 28th April 1900, contains a note by Dr Marsden, Medical Superintendent of the Monsall Fever Hospital, Manchester, on the inoculation of 14 out of 22 nurses engaged in nursing typhoid patients. Of the remaining 8, 4 had already had

typhoid. The inoculations were made in October 1899. The following table shows the subsequent freedom from typhoid of the nursing staff:—

Year.	Number of Typhoid Patients.	Cases among Nursing Staff.
1895	229	3
1896	238	3
1897	302	4
1898	426	8
To end of September 1899	163	5
From October 1899 to March 1900	146	0

2. *Ladysmith, South Africa.* The *Lancet*, 14th July 1900, contains a short note by Professor Wright, on the distribution of typhoid among the officers and men of the military garrison, during the siege of Ladysmith. The figures are as follows:—

	Number.	No. of Cases.	Proportion of Cases.	No. of Deaths.	Proportion of Deaths.	Case-mortality.
Not inoculated	10,529	1489	1 in 7.07	329	1 in 32	1 in 4.52
Inoculated .	1,705	35	1 in 48.7	8	1 in 213	1 in 4.4

The wide difference between the two groups, as regards the incidence of the disease, is well marked; but the case mortality is practically the same in each group. (The statistics of the General Hospital, Ladysmith, also tell in favour of the preventive treatment: see Surgeon-Major Westcott's letter, *British Medical Journal*, 20th July 1901, in answer to Dr Melville's letter, *British Medical Journal*, 20th April 1901.)

3. *The Portland Hospital: Modder River and Bloemfontein.* The *British Medical Journal*, 10th November 1900, contains an account by Dr Tooth of the cases of typhoid in this hospital. Concerning the preventive treatment, he says: "The experience of my colleague Dr Calverley and myself may be of interest, though we fear that the numbers are too few for safe generalisation.

"*Personnel of the Portland Hospital.* We take first the relation of disease and inoculation among the *personnel* of the hospital. Twenty-four non-commissioned officers, orderlies, and servants of the Portland Hospital, and 4 of the medical staff, were inoculated on the voyage out. All these showed the local symptoms at the time; that is, pain, stiffness, and local erythema; 17 also presented well-marked constitutional symptoms—general feeling of illness, fever, and headache. Of the orderlies, 9 had enteric fever subsequently. Two had refused inoculation, and both of these had the disease very severely; in fact one died. Of the inoculated cases, 5 had the disease lightly, and 2 fairly severely. One of the sisters had the disease rather severely, and she had not been inoculated.

"*Officers and men admitted to the Portland Hospital.* We had under treatment at the Portland Hospital 231 cases of enteric fever, most of which came under our care at Bloemfontein. We have not included in these figures a number of patients who came in convalescent for a short time only, and on their way to the base, and who would

therefore appear in the admission and discharge book of the hospital. If we did so, of course our percentages would be lower. Of these 231 patients, 53 had been inoculated at home or on the voyage out, and of them 3 died, making a percentage of deaths among the inoculated of 5.6 per cent.; 178 had not been inoculated, of whom 25 died; that is, a mortality among the non-inoculated of 14 per cent. The general mortality in enteric fever with us was 28 deaths out of 231 cases: that is, 12.1 per cent., which seems to compare favourably with the experience of the London hospitals.

"It is interesting to record our experience among the officers taken separately. Thirty-three officers were admitted with enteric fever; 21 had been inoculated; that is, 63.6 per cent., a much larger percentage than among the men. Only one of these officers died, and he had not been inoculated.

"These figures are small, but such as they are they are significant, and they dispose us to look with favour upon inoculation. So also does our clinical experience with our patients, for among the inoculated the disease seemed to run a milder course."

4. *No. 9 General Hospital, Bloemfontein.* The *Medical Chronicle* for January 1901 contains an account, by Dr J. W. Smith, of the work of this hospital. He says: "The general impression amongst the medical officers in our hospital was that a single inoculation probably did not confer an immunity lasting very long—the lapse of time differ-

ing in individuals — and also that there was a tendency in the cases of enteric in inoculated patients to abort at the end of ten or fourteen days. I should say, however, that a very considerable number of our detachment who had been inoculated suffered from enteric, of whom 4 at least died. Of the medical staff, the only member of the junior staff who had not been inoculated died of enteric."

5. *Scottish National Red Cross Hospital, Kroonstadt.* The *British Medical Journal*, 12th January 1901, contains an account of the work of this hospital by Surgeon-Colonel Cayley, Officer in Charge. He says: "The first section of the hospital, consisting of 61 persons—officers, nursing sisters, and establishment—left Southampton on 21st April 1900. During the voyage out, all except 4 were inoculated twice, at an interval of about ten days; 2 were inoculated once; and 2 (who had had typhoid) were not inoculated. Immediately we reached the Cape, the hospital was sent up to Kroonstadt in the Orange River Colony, and remained there as a stationary hospital till the middle of October. During this period there were always many cases of enteric under treatment in hospital. Further, some of the medical officers and student-orderlies had charge of the Kroonstadt Hotel temporary hospital, which was crowded up with enteric cases; and the nursing sisters, for three weeks, did duty in the military hospitals at Bloemfontein in May and June, when enteric fever was at its worst. There was not a

single case of enteric among the *personnel* of this first section of the hospital.

The second section of the hospital—medical officers, nurses, and establishment, 82 in all—left Southampton in May 1900. On board ship nearly all of them were inoculated, but many of them only once. The material for inoculation had been on board for some time, and was not so fresh as in the first instance. Of this second section, 1 nurse had enteric at Kroonstadt. She was the only one, out of a total of 36 nurses, who suffered from enteric; and she was the only nurse who was not inoculated, excepting the 2 who were protected by a previous attack of enteric. A third section of the hospital, consisting of 4 medical officers and 16 nurses, went out in July; they were all inoculated, and none of them had enteric.

"Of the second section, 5 orderlies had enteric fever at Kroonstadt, of whom 2 died. Of these 5, there were 2 inoculated (once) and 3 non-inoculated. Of the 2 who died, 1 had been once inoculated, the other had not been inoculated."

6. *Meerut, India.* The *British Medical Journal*, 9th February 1901, gives a short note by Professor Wright on inoculations in the 15th Hussars. He says: "Through the kindness of Lieutenant-General Sir George Luck, commanding the Bengal Army, I am permitted to publish the following officially compiled statistics, dealing with the effects of antityphoid inoculations in the case of the 15th Hussars:—

From 22nd October 1899 to 22nd October 1900.

	Strength.	Inoculated.	Cases.	Deaths.	Not Inoculated.	Cases.	Deaths.
Officers . . .	22	19	0	0	3	0	0
N.C.O. and Men . .	481	317	2	1	164	11	6
Women . . .	36	24	0	0	12	0	0

It would thus appear that the incidence of enteric in the inoculated was represented by 0.55 per cent., and the mortality by 0.27 per cent.; while the incidence in the uninoculated was 6.14 per cent., and the death-rate 3.35 per cent."

If the inoculated had suffered equally with the uninoculated, they would have had 22 cases with 11 deaths, instead of 2 cases with 1 death.

7. *The Edinburgh Hospital, South Africa.* The *Scottish Medical and Surgical Journal*, March 1901, contains an account of the work of the Edinburgh Hospital, by Dr Francis Boyd. Of the staff, 58 were inoculated (27 once, and 31 twice). Among these 58, there were 9 cases of typhoid fever, with 1 death, in a patient who had old mitral disease. "Our experience has been that, while inoculation appears to modify the disease, completely modified attacks are met with in the uninoculated. Again, very severe attacks, with complications and relapse, occur in those who have been inoculated. One cannot from this conclude that inoculation has been valueless, for had not the patient been inoculated, the attack might have been still more severe."

8. *Egypt and Cyprus.* The *British Medical Journal*, May 4th 1901, gives a short note by Professor Wright on inoculations during 1901 in Egypt and Cyprus. He says: "I am indebted to the kindness of Colonel W. J. Fawcett, R.A.M.C., Principal Medical Officer in Egypt, for the following statistics dealing with the incidence of enteric fever, and the mortality from the disease, for the year 1900, in the inoculated and uninoculated among the British troops in Egypt and Cyprus:—

	Average Annual Strength.	Cases.	Deaths.	Percentage of Cases.	Percentage of Deaths.
Uninoculated	2669	68	10	2.50	0.40
Inoculated .	720	1	1	0.14	0.14

These figures testify to a nineteen-fold reduction in the number of attacks of enteric fever, and to a threefold reduction in the number of deaths from that disease, among the inoculated. . . . The only case which occurred among the inoculated was that of a patient admitted to hospital on the thirty-third day after inoculation. It would seem that the disease was in this case contracted before anything in the nature of protection had been established by the inoculation."

9. *Imperial Yeomanry Hospital, Pretoria.* Dr Rolleston, Consulting Physician to this hospital, writes in the *British Medical Journal*, 5th October 1901, "Among the *personnel* of the hospital (17 medical officers, 50 nursing sisters, and 83 orderlies, etc.), total, 150, there were 22 cases of enteric fever,

or an incidence of 14.6 per cent. Of the 150, 35 were inoculated, and of these, 6, or 17 per cent., suffered from enteric; while, of 115 non-inoculated members of the *personnel*, 16, or 13.9 per cent., suffered from enteric fever; the percentage is therefore higher among the inoculated. There were 2 deaths, both in non-inoculated patients. In 100 cases of enteric fever among non-commissioned officers and men, taken mainly from convalescent patients, only 8 had been previously inoculated; there were 3 fatal cases, all among non-inoculated patients. Among 42 officers who had enteric, no fewer than 19 had been previously inoculated; 6 of these 19 cases were severe in character, but none were fatal; of the 23 non-inoculated cases, 7 were severe, and of these 7, 3 ended fatally. The interval between inoculation and the subsequent incidence of enteric fever varied between one and twenty-one months, but in only four instances was the interval less than six months. The average interval between inoculation and the onset of enteric fever in these 19 cases was thirty-eight weeks.

As far as these scanty figures go, they point to the conclusion (1) that antityphoid inoculation does not absolutely protect against a future attack of typhoid fever; (2) that when enteric occurs in an inoculated person, there is, as a rule, an interval of about six months; (3) that inoculation protects against a fatal termination to the disease.

10. *Richmond Asylum, Dublin.* The *British Medical Journal*, 26th October 1901, contains a note by Professor Wright on an outbreak of typhoid

in this asylum during August–December 1900. Inoculations were begun on 6th September, by Dr Cullinan, and by 30th November 511 persons were inoculated. After careful criticism of all doubtful cases, Professor Wright gives the following figures :—

Comparative Incidence of Typhoid Fever in Inoculated and Non-Inoculated, calculated upon the average strength of the representative groups during the period intervening between the commencement of the inoculations and the termination of the epidemic.

	Average Strength.	Cases.	Deaths.	Percentage of Cases.	Percentage of Deaths.
Uninoculated	298	30 (– 1 ?)	4	10.1	1.3
Inoculated ' .	339	5 (+ 1 ?)	1	1.3	0.3

"It may be noted," he says, "that the result is in conformity with that of all the statistical returns of antityphoid inoculation which have reached me."

11. *Deelfontein.* The *Lancet*, 18th January 1902, contains a paper by Dr Washbourn and Dr Andrew Elliot, on 262 cases of typhoid fever in the Imperial Yeomanry Hospital at Deelfontein during the year March 1900 to March 1901. (See Dr Washbourn's earlier letter, *Brit. Med. Jour.*, 16th June 1900.) They say: "In 211 of our cases, it was definitely recorded whether the patient had been inoculated or not: 186 of these cases had not been inoculated, with 20 deaths, or a mortality of 10.7 per cent; 25 had been inoculated with 4 deaths, or a mortality of 16 per cent. The mortality was thus higher among the inoculated than among the

non-inoculated." Of the *personnel* of the hospital, there were 59 inoculated, with 4 cases, and 25 not inoculated, with 4 cases.

12. *Winburg.* The *Lancet*, 5th April 1902, contains a short note by Professor Wright, on the 5th Battalion, Manchester Regiment. He says: "In view of the dearth of statistics bearing on the incidence of typhoid fever in South Africa in inoculated and uninoculated persons respectively, the following, for which I am indebted to Lieutenant J. W. West, R.A.M.C., Winburg, Orange River Colony, may not be entirely without interest. The statistics here in question give the results obtained in the case of the 5th Battalion, Manchester Regiment, for the six months which have elapsed since their landing in South Africa. The figures, which relate to a total strength of 747 men and officers under observation, are as follows:—

	Number.	Cases.	Deaths.	Percentage of Cases.	Percentage of Deaths.
Uninoculated	547	23	7	4.2	1 in 3.3
Inoculated .	200	3 .	0	1.5	0

"The three attacks in the inoculated are reported to have been of exceptionally mild type, contrasting in a striking manner with the severe attacks which occurred in the uninoculated. At the time of sending in the report, some of the uninoculated patients were 'not yet out of danger.'"

Certainly, these instances show a good balance of lives saved, not only under the adverse conditions of the war, but also in Egypt, India, and the United Kingdom. But the bacteriological work on typhoid fever has been directed also to the working out of a very different problem: and that is the method of diagnosis which is called "Widal's reaction." The practical uses of this reaction are of the utmost importance. It is the outcome of work in different parts of the world—by Wright and Semple and Durham in England, Chantemesse and Widal in France, Pfeiffer and Kolle and Grüber in Germany, and many more. The first systematic study of it was made by Durham and Pfeiffer; and Widal's name is especially associated with the application of their work to the uses of practice. Admirable accounts of the whole subject are given by Dr Cabot in his book, *The Serum-Diagnosis of Disease* (Longmans, 1899), and by Mr Foulerton in the *Middlesex Hospital Journal*, October 1899 and July 1901.

Widal's reaction is surely one of the fairy-tales of science. The bacteriologist works not with anything so gross as a drop of blood, but with a drop of blood fifty or more times diluted; one drop of this dilution is enough for his purpose. Take, for instance, an obscure case suspected to be typhoid fever: a drop of blood taken from the finger is diluted fifty or more times, that the perfect delicacy of the test may be ensured; a drop of this dilution is mixed with a drop of nutrient fluid containing living typhoid bacilli, and a drop of this mixture

of blood and bacilli is watched under the microscope :—

"The motility of the bacilli is instantaneously or very quickly arrested, and in a few minutes the bacilli begin to aggregate together into clumps, and by the end of the half-hour there will be very few isolated bacilli visible. In less marked cases, the motility of the bacilli does not cease for some minutes : while in the least marked ones the motility of the bacilli may never be completely arrested, but they are always more or less sluggish, while clumping ought to be quite distinct by the end of the half-hour."

The result of this clumping is also plainly visible to the naked eye, by the subsidence of the agglutinated bacteria to the bottom of the containing vessel : and thus an easy practical mode of diagnosis is afforded by it.

As with typhoid, so with Malta fever, cholera, and some other infective diseases. And the unimaginable fineness of this reaction goes far beyond the time of the disease. Months, even years, after recovery from typhoid, a fiftieth part of a drop of the blood will still give Widal's reaction : and it has been obtained in an infant whose mother had typhoid before it was born. A drop of dried blood, from a case suspected to be typhoid, may be sent a hundred miles by post to be tested ; and typhoid, like diphtheria, may now be submitted to the judgment of an expert far away, and the answer telegraphed back. It would be difficult to exaggerate the practical importance of this reaction

for the early diagnosis of cases of typhoid fever, especially those cases that appear, at the onset, not severe.

Malta Fever.

The specific organism of Malta fever (Mediterranean fever), the *bacillus Melitensis*, was discovered in 1887 by Surgeon-Major David Bruce, of the Army Medical Staff. Its nature and action were proved by the inoculation of monkeys. The use of Widal's reaction is of great value in this disease :—

"The diagnosis of Malta fever from typhoid is, of course, a highly important practical matter. It is exceedingly difficult in the early stages." (Manson, *loc. cit.*)

As with typhoid, so with Malta fever, Netley led the way to the discovery of an immunising serum. In the course of the work, one of the discoverers was by accident infected with the disease :—

"He was indisposed when he went to Maidstone to undertake antityphoid vaccination, and after fighting against his illness for some days, he was obliged to return to Netley on 9th October. Examination of blood-serum (Widal's reaction) showed that he was suffering from Malta fever. It appears that he had scratched his hand with a hypodermic needle on 17th September, when immunising a horse for the preparation of serum-protective against Malta fever; and his blood, when

examined, had a typical reaction on the micrococcus of Malta fever in 1000-fold dilution. The horse, which has been immunised for Malta fever for the last eight months, was immediately bled, and we are informed that the patient has now had two injections, each of 30 cub. cm. of the serum. He is doing well, and it is hoped that the attack has been cut short." (*British Medical Journal*, 16th October 1897.)

About fifty cases had up to September 1899 been treated at Netley "with marked benefit: whereas they found that all drug-treatment failed, the antitoxin treatment had been generally successful."* A good instance of the value of the serum-treatment of Malta fever is published in the *Lancet*, 15th April 1899. For a later account of this treatment and of its efficacy, see the *Philadelphia Medical Journal*, 24th November 1900.

* For the whole subject, see *Lancet*, 9th September 1899, paper by Surgeon-Major Birt and Surgeon-Captain Lamb. Two other cases of accidental inoculation occurred at Netley.

X

THE MOSQUITO: MALARIA, YELLOW FEVER, FILARIASIS

WITHIN the last few years, it has been proved that the mosquito is an intermediate host, between man and man, of malaria, yellow fever, and filariasis (elephantiasis).* Just as the grosser parasites, the tape-worms, must alternate between man and certain animals, and cannot otherwise go through their own life-changes and reproduce their kind, so the micro-parasites that are the cause of malaria, etc., alternate between man and the mosquito, having the mosquito as an intermediate host. These organisms, once they get into the mosquito, pick out certain structures, and there carry out a definite cyclical phase of their lives, whereby their progeny make their way into the stylets of the mosquito, and so get back to man, who is their "definitive host." Thus, malaria is not, strictly speaking, a disease of man; it is one phase in man of micro-organisms that have another

* For Dr Graham's recent experiments at Beyrout, which seem to prove that the mosquito can also convey dengue or dandy-fever, see the *New York Medical Record*, 8th February 1902.

phase in mosquitoes. So also with filariasis; the filariæ in man, their ova, and their embryo-worms, are one phase of filariasis; and the embryo-worms in certain structures of the mosquito are another phase. The *plasmodium malariæ* and the *filaria* are instances of a law of animal life that holds good also of plant life:—

"All plants and animals possess parasites, and thousands of different species of parasites have been closely studied by science; we therefore know much about their general ways of life. As a rule, a particular species of parasite can live only in the particular species of animal in which, by the evolution of ages, it has acquired the power of living. It is therefore not enough for the parasites of an individual animal—say a man—to be able to multiply within that individual, but they must also make arrangements, so to speak, for their progeny to enter into and infect other individuals of the same species. They cannot live for ever in one individual; they must spread in some way or other to other individuals.

"The shifts made by parasites to meet this requirement of their nature are many and various, and constitute one of the wonders of nature. Some scatter their spores and eggs broadcast in the soil, water, or air, as it were in the hope that some of them will alight by accident on a plant or animal suitable for their future growth. Many parasites employ, in various ways, a second species of animal as a go-between. Thus, some tape-worms, and the worms which cause trichinosis, spend a part of their lives in the flesh of swine, and transfer themselves to human beings when the latter eat this flesh.

To complete the cycle, the parasites return to swine from human offal; so that they propagate alternately from men to swine, and from swine to men. The blood-parasites which cause the deadly tsetse-fly disease among cattle in South Africa are transferred from one ox to another on the proboscis of the ox-biting tsetse-fly. The progeny of the flukes of sheep enter a kind of snail, which spread the parasites upon grass. The progeny of the guinea-worm of man enter a water flea. The progeny of the parasites which cause Texas cattle-fever, and which are very like the malarial parasites, live in cattle-ticks, and are transferred by the young of these ticks into healthy cattle." (Ross, *Malarial Fever*, 1902.)

It has further been discovered, that of the many species of mosquitoes or gnats, *Anopheles* is the go-between of malaria, and *Culex* of yellow fever and filariasis. For want of space here, the facts relating to filariasis must be left out. They are given in Manson's *Tropical Diseases* (second edition, 1900), and in the reports of the Nigerian Expedition of the Liverpool School (1901).

1. Malaria.

The *plasmodium malariæ* was discovered by Laveran in 1880, in the blood of malarial patients. For many years his work stopped there, because it was impossible to find the *plasmodium* in animals: "the difficulties surrounding the subject were so great that this discovery seemed to be almost hopeless." In 1894, Dr Patrick Manson—who had proved mosquitoes to be the intermediate host in the

case of the parasitic nematode *filaria*—suggested, as a working theory of malaria, that the plasmodium was carried by mosquitoes. This belief, not itself new, he made current coin. He observed that there is a flagellate form of the plasmodium, which only comes into existence after the blood has left the body: and he suggested that the flagella might develop in the mosquito as an intermediate host, a halfway-house between man and man. Then, in 1895, Surg.-Maj. Sir Ronald Ross, I.M.S., set to work in India, keeping and feeding vast numbers of mosquitoes on malarial blood; and for two years without any conclusive result. About this time came MacCallum's observations, at the Johns Hopkins University, on a parasitic organism, *halteridium*, closely allied to the plasmodium malariæ; he showed that the flagella of the halteridium are organs of impregnation, having observed that the non-flagellated form, which he regarded as the female, after receiving one of the flagella, changed shape, and became motile. In August 1897, Sir Ronald Ross found bodies, containing pigment like that of the malarial parasite, in the outer coat of the stomach of one kind of mosquito, the grey or dapple-winged mosquito, that had been fed on malarial blood. In February 1898, he was put on special duty under the Sanitary Commissioner with the Government of India, to study malaria, and started work again in Calcutta :—

"Arriving there at a non-fever season, he took up the study of what may be called 'bird malaria.'

In birds, two parasites have become well known—(1) the halteridium, (2) the proteosoma of Labbé. Both have flagellated forms, and both are closely allied to the plasmodium malariæ. Using grey mosquitoes and proteosoma-infected birds, Ross showed by a large number of observations that it was only from blood containing the proteosoma that pigmented cells in the grey mosquito could be got; therefore that this cell is derived from the proteosoma, and is an evolutionary stage of that parasite. Next, Ross proceeded to find out its exact location, and found that it lay among the muscular fibres of the wall of the mosquito's stomach. It grows large (40-70 micromillimetres) and protrudes from the external surface of the stomach, which under the microscope appears as if covered with minute warts." (Manson, at Edinburgh meeting of British Medical Association, 1898.)

These pigmented spherical cells give issue to innumerable swarms of spindle-shaped bodies, "germinal rods"; and in infected mosquitoes Ross has found these rods, in the glands that communicate with the proboscis. Thus the evidence appeared complete, that the plasmodium malariæ, like many other parasites, had a special intermediate host for its intermediate stage of development; and that this host was the dapple-winged mosquito. It is impossible to over-estimate the infinite delicacy and difficulty of Ross's work; for instance, in his "Abstract of Recent Experiments with Grey Mosquitoes,' he says that "out of 245 grey mosquitoes fed on birds with proteosoma, 178, or 72 per cent., contained pigmented cells; out of 249 fed on blood

containing halteridium, immature proteosoma, etc., not one contained a single pigmented cell." Another time (April 1898) he counted these pigment-cells under the microscope :—

"Ten mosquitoes fed on the sparrow with numerous proteosoma contained 1009 pigmented cells, or an average of 101 each. Ten mosquitoes fed on the sparrow with moderate proteosoma contained 292 pigmented cells, or an average of 29 each. The mosquitoes fed on the sparrow with no proteosoma contained no pigmented cells."

Finally, he completed the circle of development by infecting healthy sparrows by causing mosquitoes to bite them.

In 1899, there went out a German Commission to German East Africa, a Royal Society's Commission to British Central Africa, and an expedition from the Liverpool School of Tropical Medicine; in 1900, another German Commission, this time to the East Indies, and another expedition from the Liverpool School; by July 1901, the Liverpool School was organising its seventh expedition. Italy, of course, has given infinite study to the disease :—

"It has been decided that, in addition to the stations of observation and experiment in the provinces of Rome, Milan, Cremona, Mantua, Gercara, Foggia, Lecce, others shall be established in the provinces of Udine, Verona, Vicenza, Padua, Ravenna, Pisa, Basilicata, and Syracuse. Besides epidemiological researches, applications on a large

scale will be made of preventive measures for the protection of the agricultural population against the scourge. Another extensive experiment on the prophylaxis of malaria will be made on the Emilian littoral. Moreover, in all the malarious regions of the Italian peninsula the provincial and communal administrations and many private persons will co-operate in the application of preventive measures. From all this it may be gathered that during the summer and autumn the war against malaria will be carried on in Italy with great vigour and thoroughness." (*British Medical Journal*, 6th July 1901.)

In India, the work started in 1900 by the Royal Society Commissioners, and by the Nagpur Conference, has been widely extended; especially by such researches as those of Major Buchanan, I.M.S., Superintendent of the Central Jail, Nagpur. The following paragraph, from the latest report of the Sanitary Commissioner with the Government of India, refers to Major Buchanan's published work, *Malarial Fevers and Malarial Parasites in India*:—

"A remarkable note is struck at the outset, in the acknowledgment made by the author of the capable assistance rendered in these researches by several of his Burmese prisoners, whom he trained to the use of the microscope, and who soon became expert in detecting and distinguishing the various kinds of parasites. . . . Besides a systematic clinical account of the different forms of fever and the associated parasites, which is the first attempt of the kind in India, there are a summary of the facts

showing the relation of the seasonal prevalence of *Anopheles* to the incidence of attacks; experiments exhibiting the protective effects of mosquito-curtains; inoculation-experiments; researches on the blood-parasites of birds; and many other points. . . . Nor can we pause to notice the many attempts now being made by health officers and others to pursue the methods of prophylaxis indicated; these efforts are necessarily in the tentative stage, but, so far, and especially where carried out in connection with small communities and institutions, they are giving promise of gratifying success."

The famous experiment made by Dr Sambon and Dr Low in 1900, must be recalled here:—

"Dr Luigi Sambon and Dr G. C. Low, both connected with the London School of Tropical Medicine, volunteered to live from June till October, that is to say, through what may be called the height of the malaria season, in a part of the Campagna near Ostia, which is so infested by the disease that no one who spends a night there under ordinary conditions escapes the effect of the poison. Dr Sambon, Dr Low, Signor Terzi, and their servants, have now exposed themselves to the pestilential influence of this valley of the shadow of death for over two months. They live in a mosquito-proof hut; they take no quinine or other drug which might be regarded as prophylactic. Not one of the experimenting party has the least sign of infection.* . . .

* Dr Patrick Manson, in the *British Medical Journal*, 29th September 1900, gives the following account of this experiment:—"A wooden hut, constructed in England, was shipped to Italy and erected in the Roman Campagna, at a

"What for practical purposes may be regarded as an experiment of the same kind, is being conducted in West Africa. Dr Elliot, a member of the Liverpool expedition sent to Nigeria some time ago to investigate the subject of malarial fever, has recently returned to this country. He reports that the members of the expedition have been perfectly well, although they have spent four months in some of the most malarious spots. They lived practically amongst marshes and other places hitherto supposed to be the most deadly. They have not kept the fever off by the use of quinine, and they attribute their immunity to the careful use of mosquito-nets at night." (*British Medical Journal*, 22nd September 1900.)

A similar "experiment," of the utmost importance, was made in 1900 by Professor Grassi. It

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spot ascertained by Dr L. Sambon, after careful inquiry, to be intensely malarial, where the permanent inhabitants all suffer from malarial cachexia, and where the field-labourers, who come from healthy parts of Italy to reap the harvest, after a short time all contract fever. This fever-haunted spot is in the King of Italy's hunting-ground near Ostia, at the mouth of the Tiber. It is waterlogged and jungly, and teems with insect life. The only protection employed against mosquito-bite and fever by the experimenters who occupied this hut was mosquito-netting, wire screens in doors and windows, and, by way of extra precaution, mosquito-nets round their beds. Not a grain of quinine was taken. They go about the country quite freely—always, of course, with an eye on *Anopheles*—during the day, but are careful to be indoors from sunset to sunrise. Up to 21st September, the date of Dr Sambon's last letter to me, the experimenters and their servants had enjoyed perfect health, in marked contrast to their neighbours, who were all of them either ill with fever, or had suffered malarial attacks."

concerned the workmen and their families along the Battipaglia-Reggio railway, 104 in all, including 33 children. The great majority of them had suffered from malaria in the preceding year; and only 11, including 4 children, had never suffered from it. Pending the arrival of the malarial season, quinine was given to all who needed it. The first *Anopheles* with its salivary glands infected was found on 14th June. Twelve days later came a case of malaria outside the "zone of experiment," in a person who had never had malaria before. The twelve days correspond to the incubation-period after infection. *Anopheles* having come, and the malarial season with him, the experiment was begun. The houses were carefully protected with wire netting, chimneys and all; the *siesta* was taken under wire netting; the workmen, if they were out in the evening or at night, wore veils and gloves; and *Anopheles* was to be killed wherever it was found. Quinine was altogether given up and forbidden, except for three workmen who had escaped or evaded its use before June, and had, indeed, never before been treated with quinine; one of them, moreover, had been sleeping outside the zone of experiment in July. Except these three, all the 104 and their doctors remained absolutely free from malaria up to 16th September, the date of Professor Grassi's report:—

"Rightly to estimate the value of these facts, it is necessary briefly to describe the surroundings of the protected area. Towards the north, coming from Battipaglia, three railway cottages are situated,

at a distance of 1, 2, and 3 kilometres respectively. The 25 inhabitants of these cottages, although they were put under the tonic and quinine treatment in the non-malarial season, all without exception were taken ill with malarial fevers, in many cases obstinate."

Experiments of voluntary exposure to bite from an infected mosquito were made at or about this time, in London, New York, Italy, and India. The London "consignment" of mosquitoes had been allowed to bite a malaria-patient in Rome. The experiment had to be very carefully planned:—

"To have sent mosquitoes infected with malignant tertian parasites might have endangered the life of the subject of the experiment; and quartan-infected insects might have conferred a type of disease which, though not endangering life, is extremely difficult to eradicate. The cases, therefore, on which the experimental insects were fed had to be examples of pure benign tertian—a type of case not readily met with in Rome during the height of the malarial season; the absolute purity of the infection could be ascertained only by repeated and careful microscopic examination of the blood of the patient." (*British Medical Journal*, 29th September 1900.)

The mosquitoes were forwarded, through the British Embassy in Rome, to the London School of Tropical Medicine. The two brave gentlemen who let themselves be bitten by some thirty of the mosquitoes were in due time attacked by malaria, and the tertian forms of the parasite were found in

their blood. Nine months later, one of them had a relapse, and the parasite was again found in his blood.

It is not possible to sum up the wealth of work on malaria published in 1900-1901. Good accounts of it are in the Transactions of the Section of Tropical Diseases, at the Annual Meeting of the British Medical Association (Cheltenham, 1901), and in the Thompson Yates Laboratories Reports, vol. iii., pt. 2, 1901. Everything had to be studied: not only the nature and action of the *plasmodium* in all its phases, but also the whole natural history and habits of the *Anopheles* of different countries; and, above all, the incidence of the disease on natives and on Europeans in China, India, and Africa. All that can be done here is to try to indicate the principal lines followed in the present world-wide campaign against malaria. The following paragraphs are taken mostly from the accounts given by Dr Christophers and Dr Annett, in the Thompson Yates Laboratories Report, 1901:—

1. *Elimination of the Infection at its Source.* This is the method employed with success by Professor Koch in New Guinea, viz., to search out all cases of malaria (the concealed ones in particular), and to render them harmless by curing them with quinine. At Stephansort, by thus hunting up all infected cases, and as it were, sterilising them by the systematic administration of quinine, he was able to achieve a great reduction of the disease in the next malarial season, even under adverse conditions. He says, in his report to the German

Government: "The results of our experiment, which has lasted nearly six months, have been so uniform and unequivocal, that they cannot be regarded as accidental. We may assume that it is directly owing to the measures we have adopted that malaria here has, in a comparatively short time, almost disappeared."

This method, of course, is applicable only in small communities; and, within these limits, it may become one of the most valuable of all methods, being, like the quality of mercy, a blessing both to him who gives and to him who takes it. But it cannot be practised on a vast scale. This difficulty is well put by Sir William MacGregor, K.C.M.G., Governor of Lagos, West Africa:—

"In all probability, the day will come before long, when newly-appointed officers for places like Lagos will have to undergo a test as to whether they can tolerate quinine or not. A man that cannot, or a man that will not, take quinine, should not be sent to or remain in a malarial country, as he will be doing so at the risk of his own life, *and to the danger of others*. . . . The great difficulty is how to extend this treatment beyond the service, more particularly to the uneducated masses of the natives. It is simply impossible to protect the whole population by quinine administered as a prophylactic. In the first place, the great mass of natives would not take the medicine; and, in the second place, the Government could not afford to pay for the 70 tons of quinine a year that would be required to give even a daily grain dose to each of 3,000,000 of people."

2. *Segregation of Europeans from Natives.* This method is strongly advocated by the members of the Nigeria Expedition of the Liverpool School (1900). The distance of removal to half a mile is considered sufficient: "Considerable evidence has now been accumulated to prove that the distance which is traversed by a mosquito is never very great, and extremely rarely reaches so much as half a mile." The arguments in favour of this method of "segregation" are of so great interest that they must be put here at some length. The drawback is that the method cannot be followed everywhere to its logical issue without some risk of giving offence, of seeming to abandon the native, of damaging commerce, and so forth. But, short of this, much might be done for the protection of Europeans in Africa :—

"This method is a corollary of the discovery that native children in Africa practically all contain the malaria parasite, and are the source from which Europeans derive malaria. Koch showed in New Guinea that in most places infection was very prevalent in native children, so much so that in some villages 100 per cent. of those examined contained parasites. He also showed that, as the children increased in age, immunity was produced, so that in the case of adults a marked immunity was present, and malarial infection was absent. The Malaria Commission showed, independently, that a condition of universal infection existed among the children of tropical Africa, associated with an immunity of the adults. This infection in children had many remarkable characteristics. The

children were in apparent health, but often contained large numbers of parasites, and a small proportion only of the children failed to show some degree of infection. . . . The Liverpool School Expedition found a similar condition of affairs in all parts of Nigeria visited by them.

"With a knowledge of the ubiquity of native malaria, the method of infection of Europeans becomes abundantly clear. The reputed unhealthiness or healthiness of stations is seen at once to be dependent on the proximity or non-proximity of native huts. The attack of malaria after a tour up-country, the malaria at military stations like Prah-su, the abundance of malaria on railways, are all explicable when the extraordinary condition of universal native infection is appreciated. It is evident that, could Europeans avoid the close proximity of native huts, they would do away with a very obvious and great source of infection. . . . When it is understood that each of these huts certainly contains many children with parasites in their blood, and also scores or hundreds of *Anopheles* to carry the infection, then the frequency with which Europeans suffer from malaria is scarcely to be wondered at. . . . The accompanying plan is that of a new railway settlement on the Sierra Leone Railway. Miles of land free from huts exist along the line, but the close neighbourhood of native huts has been selected. At the time of building of these quarters, it lay in the power of the engineers to have a malaria-free settlement; instead of which, by the non-observance of a simple fact, the station is most malarious: in this particular instance, much ingenuity has been shown in providing each set of European quarters with plenty of malarial infection. In towns only is there any difficulty in carrying out

the principle of segregation. In two instances, however, this has been carried out in towns, with the result that the segregated communities of Europeans are notoriously the most healthy on the West Coast. Even when no scheme of complete segregation can be carried out, the principle should always be borne in mind, and, whenever opportunity offers, huts should be removed, and European houses built in the open. . . . It is almost universally the rule in West Africa to find European houses built round by native quarters, a practice which long experience in India has taught Europeans to avoid carefully. At Old Calabar, many of the factories are almost surrounded, except in front, by native habitations; similarly, at Egwanga, the small native town is built by the side and back of one of the factories. Also at the Niger Company's factory at Lokoja, the native houses are very close up to the Company's boundary railings. Akassa engineers' quarters may be, again, mentioned as an example where the engineering artisans, chiefly natives of Lagos, Accra, and Sierra Leone, are housed with their families alongside the European house. A large proportion of these native children were found by us to contain malarial parasites. Similarly also at Asaba, the proximity of the barracks of the Hausa soldiers, who have their wives and children with them, is a dangerous menace to the officers at the Force House.

"Examples of the opposite condition of affairs might also be given. For instance, at Old Calabar, the Government offices and Consulate, Vice-consulate, and medical house, are comparatively free from malarial fever; it having been established that the natives shall not build on the European side of the creek separating the two slopes on which the

native town and European quarters are built. This creek is at a distance of about half a mile from the houses mentioned."

It is plain, from these and other instances given by the members of the Nigeria Expedition, that a modified sort of "segregation" can be effected in many places, without any injury either to native feelings, or to politics, or to commerce; and that by such segregation the risk of malaria among Europeans in Africa would be diminished.

3. *Protection against Anopheles.* "Grassi is of opinion," says Dr Manson, "that the malaria parasite, under natural conditions, can be acquired by man only through the bite of the mosquito, and that the mosquito can acquire the parasite only by ingesting the blood of a malaria-infected man. He holds that there is no other extracorporeal life than that described; that there is no authentic instance of malaria being acquired in uninhabited places; and that in the case of malaria in connection with soil disturbances, it depends on the creation, during digging operations, of puddles of water in which *Anopheles* breed." Manson, every page of whose book (*Tropical Diseases*, second edition, 1900) must be carefully studied on this subject, is inclined to believe that the parasite may perhaps be capable of living in the blood of other vertebrate hosts, or of passing from mosquito to mosquito; and that it may, under certain conditions, lie dormant in soil, and thus be transmitted in air, or water, or food, to workmen turning the soil. But all authorities are agreed that, practically, the fight against malaria

and the fight against *Anopheles* are one and the same thing; and the experiments by Sambon, Low, and Grassi, show what can be done, in this war against the mosquito, by way of defence. But what is practicable in Italy might not be generally practicable on the West African coast; as Sir William MacGregor says of Lagos:—

"It is not likely that in a place like Lagos as good results can be obtained from the use of mosquito-proof netting as in Italy. One great objection to it here is the serious and highly disagreeable way it checks ventilation. This is a difficulty that cannot be fully brought home to one in a cold climate. But, in a low-lying, hot, and moist locality like Lagos, it comes to be a choice of evils, to sit inside the netting stewed and suffocated, or to be worried and poisoned by mosquitoes outside. The netting is hardly a feasible remedy as regards native houses. It is not possible to protect even European quarters completely by it. Few officers or others are so occupied that they could spend the day in a mosquito-proof room. Certain it is that any man that suffers from the singular delusion that mosquitoes bite only during the night, would have a speedy cure by spending a few days, or even a few hours, in Lagos. Operations here (September 1901) are being limited to supplying one mosquito-proof room to the quarters of each officer. In this he will be able to spend the evening free from mosquitoes if he chooses to do so. The European wards of the hospital are similarly protected."

The European in Africa, as Major Ross says, is generally neglectful of his health; and the "un-

healthiness" of the African coast is to some extent due to the life that men lead there:—

"Let us compare the habits of a European in a business-house in Calcutta with the habits of a European in West Africa. In Calcutta he sleeps under a punkah or mosquito-net, or both; he dresses and breakfasts under a punkah; in the evening he takes vigorous exercise, and he dines under a punkah. He wears the lightest possible clothing, he lives in a solid, cool, airy house, and he obtains very good food; once in five or six years, he returns to Europe for leave. . . . In Africa, the houses are frequently very bad; in Freetown, for instance, they are the same as the houses of natives, and are mingled with them. The Anglo-African seems to imagine that he can live in the tropics in the same manner as he lives in England. He seldom uses a punkah, except perhaps for an hour at dinner-time, and, not seldom, he neglects even the mosquito-net. The food is often, or generally, execrable. Owing to the frequent absence of gymkanas and clubs, the exile obtains little suitable exercise."

But whatever risks the old resident may choose to take, the newcomer can at least use a proper and efficient mosquito-net at night, and avoid sleeping in a native house, and protect himself in these and the like ways against malaria.

4. *The keeping down of Anopheles.* The breeding places of *Anopheles* are ponds, swamps, and puddles, roadside ditches, tanks, and cisterns, old disused canoes, and the like collections of stagnant water: also the smaller receptacles that are more

generally occupied by *Culex*, such as broken bottles, old tins, pots, and calabashes, and barrels, whatever will hold water—all the débris and broken rubbish round huts or houses. In all these places, *Anopheles*' eggs or larvæ are found; and, with practice, it is easy to detect them. Of course, it is not easy to wage war against the adult mosquito: the work is, *Venienti occurrere morbo*, to organise gangs of workmen, or of prison labour, and "mosquito brigades"; to clear the ground of cartloads of old biscuit-tins, broken gin-bottles, and other dust-heap things, in and around the place; to cover-in the cisterns, rain-barrels, and wells; to clean pools and duck-ponds of weed, and stock them with minnows; to put a film of kerosene to the puddles, or sweep them out, or fill them up and turf them over; everywhere, to drain, and level, and clean-up the surface soil; and everywhere, by these and the like methods, to break the cycle of the life of the *plasmodium malariæ*:—

"Draining and cultivation where the land will repay the expenditure, permanent and complete flooding where it will not, and such flooding is possible; proper paving of unhealthy towns, and the filling-in of stagnant, swampy pools; these—in other words, all measures calculated to keep down mosquitoes—are the more important things to be striven for in attempting the sanitation of malarious districts. In England, in Holland, in France, in Algeria, in America, and in many other places, enormous tracts of country, which formerly were useless and pestilential, have been rendered healthy and productive by such means." (Manson, *loc. cit.*)

And, short of such great enterprises as Government works of drainage, much has already been done, in many African towns, and in India, by the work of a few men and women: not only by practical sanitary improvements, but by insistent teaching and lecturing.

Before leaving the subject of malaria, it must be added that the discovery and study of the parasite which causes it have cleared up the mystery of the specific action of quinine upon the disease. It operates simply by its germicidal effect upon the microbe. But, beyond this, we have now a clue which we never had before to guide us to the most advantageous manner of administering the drug.

2. Yellow Fever.

The specific organism of malaria may become active again and again in the blood, causing relapses twenty years or more after the original infection. The specific organism of yellow fever expends itself at once, in one acute attack; and, if the patient recovers, he is thenceforth more or less immune against infection. In the case of malaria, experiments on man were voluntarily submitted to, only to prove that *Anopheles* carries the disease: in the case of yellow fever, similar experiments were voluntarily submitted to, not only to prove that the disease is mosquito-carried, but also to obtain immunity. That the inoculation of the disease, by the application of a single mosquito recently contaminated, is calculated to produce a

mild or abortive attack less dangerous than the average attack among the non-acclimatised, was known to Finlay, and was confirmed in 1899 by the Army Commission of the United States. Except five inoculations, where evidence that the persons understood the risk incurred is unhappily wanting, it appears that no inoculation has been made save with the consent of the person inoculated. Further justification is to be found, if it is wanted, in the fact that they who made these experiments also submitted themselves to them; in the steady saving of lives that has already been begun, by methods for keeping down the mosquito that carries the disease; and in the terrible death-rate of the disease in its ordinary course:—

"It is better for women and children than for men; better for old residents than for newcomers; worst of all for the intemperate. According to a table of 293 carefully observed cases given by Sternberg, the mean mortality in the whole 293 cases was 27.7 per cent. This may be taken as a fairly representative mortality in yellow fever among the unacclimatised, something between 25 and 30 per cent, although in some epidemics it has risen as high as 50 or even 80 per cent. of those attacked. . . . Some of these epidemic visitations bring a heavy death-bill; thus, in New Orleans in 1853, 7970 people died of yellow fever; in 1867, 3093; in Rio, in 1850, it claimed 4160 victims; in 1852, 1943; and in 1886, 1397. In Havana, the annual mortality from this cause ranges from 500 to 1600 or over." (Manson, *Tropical Diseases*, 1900.)

The earlier attempts to reproduce the disease, by inoculation with its products, failed altogether :—

"In 1816, Dr Chervin, of Point-à-Pitre (Antilles), drank repeatedly large quantities of black vomit without feeling the least disturbance. Some years before, other North American colleagues, Doctors Potter, Firth, Catteral, and Parker, did everything possible to inoculate themselves with yellow fever. After having uselessly attempted experiments on animals, they experimented on themselves, inoculating the black matter at the very moment in which the moribund patient rejected it, placing this matter in their eyes, or in wounds made in their arms, injecting it more than twenty times in various parts of their body . . . in short, devising every sort of daring means for experimentally transmitting yellow fever. All these experiments were without result, and in the United States during many years it was believed that this terrible malady was non-contagious." (Sanarelli, quoted in *British Medical Journal*, 3rd July 1897.)

The history of the subject, from 1812 to 1880, is given by Dr Finlay of Havana, in the *New York Medical Record* (9th February 1901). In 1880, two very important reports on the disease were published; one by a Havana Commission of the National Board of Health of the United States, the other by the United States Navy Department. They tended to show that yellow fever is a "germ-disease"; that it is not wind-borne; and that there may be some change, outside the body of the patient, whereby the virulence of the active principle

of the disease is heightened. From these reports, Dr Finlay advanced his doctrine that the mosquito receives and transmits the germs of the disease :—

"It was upon the above line of reasoning (in these reports) that I conceived the idea that the yellow-fever germ must be conveyed from the patient to the non-immunes by inoculation, a process which could be performed in nature only through the agency of some stinging insect whose biological conditions must be identical with those which were known to favour the transmissibility of the disease."

In 1881 he inoculated himself and six soldiers with infected mosquitoes, and obtained, as he had calculated, mild attacks and subsequent immunity. During the years 1881-1900, he inoculated by this method 104 persons :—

"In these inoculations, be it remembered, my principal object was rather to avoid than to seek the development of a severe attack; in point of fact, only seventeen showed any appreciable pathogenic effects after their inoculation. I felt sure, however, that severe or fatal result might follow an inoculation either with several mosquitoes contaminated from severe cases of the disease, or from a single insect applied several days or weeks after its contamination; having come to this last conclusion, in view of the facts connected with the *Anne Marie*, and the epidemic of Saint Nazaire."

Dr Finlay's discovery that the mosquito can convey yellow fever, and that the germ of the

disease is more virulent after a prolonged sojourning in the mosquito, was proved beyond all question by the work of 1899-1901. But, so far as immunisation is concerned, few people would submit themselves to be bitten by an infected mosquito, even with perfect assurance that the germs contained in it were of a low degree of virulence: the urgent need, therefore, was for an immunising serum. In 1896, at Flores, Sanarelli discovered the *bacillus icteroides*; and by October, 1897, he had prepared an immunising serum which was able to give a considerable amount of protection to animals. He says of it, in the *Annales de l'Institut Pasteur*, October 1897 :—

"This serum was tried, directly after it had been obtained, on guinea-pigs, against a mortal dose of virulent cultures. Half a cubic centimetre of this serum, injected 24 hours before the dose of virulent cultures, gave immunity. Two centimetres of it succeeded in saving guinea-pigs already ill, even if it were injected 48 hours afterward. These doses are still far from representing the full preventive and curative power of the serum, especially if one takes count of the power of the other sera prepared up to the present time. . . .

"Such are the results hitherto obtained by laboratory work on the specific treatment of yellow fever. The preventive and curative power of the serum of the guinea-pig, the dog, and the horse, vaccinated against the bacillus icteroides, should be held as absolutely demonstrated in the case of animals."

Next year (*Annales de l'Institut Pasteur*, May

1898) came the news that he had advanced against yellow fever with its own weapons—*Premières expériences sur l'emploi du sérum curatif et préventif de la fièvre jaune.* Of the first 8 cases treated (Rio de Janeiro), 4 recovered. Then came the 22 cases at San Carlos do Pinhal, in Saint-Paul au Brésil (January 1898), with 16 recoveries, and only 6 deaths. And it is to be noted that he submitted his method of treatment to the utmost test that was possible; he chose the bad cases, and the country where the fever was most fatal:—

"Chaque cas était choisi de commun accord entre nous, dans le but de mettre bien en évidence l'action thérapeutique du sérum, *mettant toujours de côté tous les cas qui se présentaient avec des symptômes vagues ou attenuès ou en forme légère ou fruste. On ne conservait donc que des cas où, d'après la violence des phénomènes d'invasion, on devait considérer comme très peu probable une crise spontanée de la maladie.* . . .

"L'État de Saint-Paul, le plus riche de la République brésilienne, pays d'immigration, traverse aujourd'hui une triste période, depuis que la fièvre jaune, qui jusqu'à ces dernières années n'avait pas quitté les côtes, s'est diffusée et a envahi comme un incendie presque toutes les villes et presques tous les villages de l'intérieur, semant des ruines partout.

"La fièvre jaune est bien plus grave à l'intérieur du pays, et atteint une mortalité bien plus élevée que celle qu'on observe dans les côtes, par exemple, à Rio de Janeiro, à Santos, ou à Pernambuco. Dans ces dernières villes, les immigrants en général

ne séjournent pas ; la fièvre jaune atteint en général des indigènes, ou tout au moins des gens relativement *acclimatés* par un séjour plus ou moins long, et la mortalité ne dépasse pas 50 à 60 % des malades. Dans l'intérieur du pays, au contraire, la maladie trouve un élément neuf, européen, récemment arrivé, non encore habitué au climat et au genre de vie des pays intertropicaux, et par suite extrêmement faible et sans défense. *La mortalité est d'alors* 80 *ou* 90 % *des malades*, et il y a eu à Campinas, à Rio-Claro, à Araraquara, et sur d'autres points, des épidémies comparables seulement aux invasions légendaires de la peste au moyen âge."

The serum used by Sanarelli at San Carlos came from three animals, two horses and an ox, that he had long kept immunised. He had tested it on animals, and on himself. At the isolation hospital he found only two children :—

"La plupart des gens préféraient rester chez eux pour mourir ; les seuls malades à ce moment à l'hôpital étaient deux enfants nommés Louis et Assunta del V. . . . ramassés dans la maison où leur père était déjà mort de fièvre jaune. Ces deux petits malades présentaient les symptômes caractéristiques de la maladie, y compris le *vomito negro.* Louis était au second jour et Assunta au troisième de la maladie. Ils furent soumis de suite au traitement, dont les résultats furent presque immédiats ; la fièvre et l'albuminurie disparurent, les symptômes généraux s'atténuèrent et les deux enfants entrèrent en franche convalescence."

Furthermore, Sanarelli was able to show the preventive value of the serum. At the end of

February 1898, yellow fever broke out in the jail at San Carlos :—

"La première victime fut un condamné, qui vivait avec tous les autres dans une salle où les conditions hygiéniques étaient assez mauvaises. Le lendemain, la sentinelle, qui était en rapport continuel avec la salle des condamnés, tombait malade. Quelques jours après, un autre condamné suivait le sort du premier, et bientôt un quatrième cas, mortel aussi, finit par signaler la prison comme un nouveau foyer d'infection qui venait s'allumer au centre d'un quartier de la ville encore resté indemne.

"Si on avait abandonné la chose à elle-même, on aurait vu se produire le même spectacle qu'avaient fourni, dans les conditions identiques, pendant les dernières épidémies, les prisons de Rio-Claro, de Limeira, et d'autres villes de l'État de Saint-Paul."

Every prisoner, except one who had already had the fever, was therefore given the preventive treatment. At once the outbreak stopped; no more cases occurred, though only a weak serum was used, though the state of the prison and its occupants was unhealthy, though the fever, two months later, was still raging, round the prison, in the town.

That Sanarelli did, as a matter of fact, obtain these good results with his serum treatment, is not denied: but some more recent authorities take the *bacillus icteroides* to be a secondary invader in the disease, and not the specific organism of the disease.

In October 1900, the United States Commission on Yellow Fever published a preliminary report on 11 cases of mosquito-inoculation. Of

these, the majority gave a negative result, and were found susceptible to infection, at a later date, from the blood of a yellow-fever patient. Two gave a positive result. In the course of these experiments, Dr Lazear, a member of the Commission, died of the disease. In February 1901, and again in July, the Commission published further reports, emphasising the fact that the mosquito conveys the disease, and denying that the disease can be conveyed in clothing, bedding, and so forth :—

"Our observations appear to demonstrate that the parasite of this disease must undergo a definite cycle of development in the body of the mosquito before the latter is capable of conveying infection. This period would seem to be not less than twelve days.

"We also consider the question of house infection, and are able to show that this infection is due to the presence of mosquitoes that have previously bitten yellow-fever patients; and that the danger of contracting the disease may be avoided in the case of non-immune individuals who sleep in this building, by the use of a wire screen.

"We also demonstrate, by observations made at this camp (Fort Lazear), that clothes and bedding contaminated by contact with yellow-fever cases, or by the excreta of these cases, is absolutely without effect in conveying the disease."

In February 1901, Dr H. E. Durham published an abstract of an *interim* report of the Liverpool School Yellow Fever Commission. He and Dr

Walter Myers, the two Commissioners, had both of them been attacked by the disease, and Dr Myers had died of it. The report gives evidence that the disease is due to a bacillus which is not the *bacillus icteroides;* and it does not wholly favour the earlier report (1900) of the American Commission. A later Commission to New Orleans, September 1901 to January 1902, has reported an extensive series of investigations, which seem rather to support the belief that the *bacillus icteroides* is the cause of the disease.

Immunisation, by the direct use of an infected mosquito, may be compared with the old custom of inoculation against smallpox. The use of Sanarelli's serum-treatment has not gone far. There remains for consideration the method of keeping down infection by keeping down *Culex.*

Three reports, in 1901-1902, come from Dr Guitéras (Havana), Surgeon-Major Gorgas, chief sanitary officer (Havana), and the Commission at New Orleans. Dr Guitéras reports that 6 cases of yellow fever (inoculation) were treated in a large "mosquito-proof" building, which also contained cases of other diseases. No prophylaxis was enforced, save the exclusion of mosquitoes; non-immunes visited the yellow fever cases, non-immunes nursed them, and most of the attendants and labourers about the place were non-immunes; but not a single case of infection occurred. The

New Orleans Commission reports that, of 200 cisterns, etc., examined in the city for the presence of larvæ, the larva of *Culex* (*Stegomyia*) predominated in more than 60 per cent.

The report of Surgeon-Major Gorgas is very pleasant reading. For two centuries, Cuba had been cursed with yellow fever; then, after the war with Spain, America took it over:—

"The army took charge of the health department of Havana, when deaths (from all causes) were occurring at the rate of 21,252 per year. It gives it up, with deaths occurring at the rate of 5720 per year. It took charge, with smallpox endemic for years. It gives it up, with not a case having occurred in the city for over eighteen months. It took charge, with yellow fever endemic for two centuries — the relentless foe of every foreigner who came within Havana's borders, which he could not escape, and from whose attack he well knew every fourth man must die. The army has stamped out this disease in its greatest stronghold."

Make fair allowance for the wide variation, from year to year, of the number of yellow fever cases in any town within the geographical belt of the disease; admit that a town may, in the course of nature, have many hundred cases in one year, and only half a dozen in another year. Again, make fair allowance for all other good influences of the American occupation of Cuba, beside those that were concerned with the stamping out of *Culex*; admit that the general death-rate of Havana, in

the last February of Spanish rule (1898), was 82.32 per thousand, and in February, 1901, was 19.32. Still, there is an example here, in the 1901 work in Havana, for the world to follow, wherever yellow fever exists. The following abstract of Surgeon-Major Gorgas' results has lately been published in the *Practitioner*, May 1902, by Professor Hewlett, one of the foremost of English bacteriologists :—

"Commencing in February 1901, orders were issued that every suspected case of yellow fever should be screened with wire gauze at the public expense, so as to render the room or rooms mosquito-proof. All mosquitoes in the infected house and in contagious houses were destroyed. After the middle of February, 100 men were employed in carrying out the destruction of the mosquito-larvæ in their breeding places, putting oil in the cesspools of all houses, clearing the streams, draining pools, and oiling the larger bodies of water. Up to June, quarantine was enforced, together with disinfection of the house and fomites. After that, however, rigid quarantine of the patient was stopped, and disinfection of fabrics and clothing ceased. It was merely required that the patient should be reported, his house placarded and screened, and a guard placed over each case to report how general sick-room sanitation was carried out, to see that the screen-door communicating with the screened part of the house was kept properly closed, and to see that communication with the sick-room was not too free, four or five non-immunes only being allowed in. *By the end of September, the last focus of the disease had been got rid of, and since then, up to the*

beginning of January, there has not been a single case. Whereas, for the years since 1889, from 1st April to 1st December, yellow fever caused an average of 410.54 deaths, with a maximum of 1175 for 1896, and a minimum of 79 for 1899, *it caused in* 1901 5 *deaths only. In the months of October and November, when the disease has hitherto been exceedingly rife in Havana, there has not been a single case. For the first time in* 150 *years, Havana has been free from yellow fever.*"

Thus, in a few years, from experiments on mosquitoes, sparrows, and men, has come the present plan of campaign against malaria, yellow fever, and filariasis; that is, against *Anopheles* and *Culex.* He who would know what is being done to check these diseases in Italy, India, China, Africa, and America, must read Major Ross' *Malarial Fever, its Cause, Prevention, and Treatment* (1902), and *Mosquito Brigades, and how to organise them* (1902). There has been nothing like it since Pasteur died. Far and wide, from Staten Island to Cuba, from Hong Kong to Lagos, the work of keeping down the larvæ of *Anopheles* and *Culex* is going on. *Henceforth we have to reckon not with a nameless something, but with a definite parasite, whose conditions of life are known. Before all things, we must shut off the sources of the infection.* For centuries, men had believed in exhalations and miasmata lying all over the land: and, behold, the agents of malaria are in the puddles round a man's house, and the

agents of yellow fever are in the water-butt and the broken bottles and old sardine-tins. Science has given the word, and now there are *Anopheles* brigades and *Culex* brigades set going; labourers with brooms and rubbish-carts, sweeping-out the stagnant pools, draining the surface soil, and carrying off the odd receptacles that serve to hold mosquito eggs and larvæ. The job, like all sanitary jobs, must be steady, year in year out: it must be limited to infected places, a whole continent cannot be treated. But there the work is, and will grow; and saves, by unskilled labour, and at a trivial expense, those "non-acclimatised" lives that have hitherto been thrown away as recklessly as the larvæ that are now swept out of the puddles and ditches round African settlements.

A recent report of great interest, from Barbadoes, has been published in the *British Medical Journal* for 14th June 1902. It is written by Dr Low, whose experiment on himself in the Campagna has already been noted in this chapter. Dr Low reports that there is no indigenous malaria in the island, and that neither he nor Mr Lefroy could find a single *Anopheles* larva, though they hunted diligently in the swamps and other likely places. But filariasis is terribly common, and so is *Culex fatigans*. Dr Low examined the night-blood of 600 cases of all kinds in the General Hospital, the Central Almshouse, and elsewhere, and found the filaria-embryos in no less than 76 = 12.66 per cent. He caught and dissected a hundred mosquitoes (*Culex fatigans*) from the wards and corridors of

the General Hospital, and found that no less than 23 of them were infected. If it were not for *Culex*, and for men's indifference and apathy, filariasis could be kept down all over the island:—

"There is a perfect water supply, and people can get their water fresh from the standpipes at their doors. Old wells ought to be filled up; no water-barrels or tubs should be allowed, or, if kept, they should be emptied every week or so. Tanks and collections of water in gardens should all be periodically treated with kerosene, or be furnished with closely-fitting covers to prevent mosquitoes getting in. These methods are simple and inexpensive, and each householder should see that they are applied in his garden and grounds. The difficulty begins when one has to take into account the inability of the negro to grasp anything of a hygienic nature. The only way to get over this, would be a system of sanitary inspection by a few competent men. For individual prophylaxis, mosquito-nets ought always to be used; but many, even educated people, still persist in sleeping without them; of course, nothing in this line can be expected of the native population.

"If such means were adopted for Barbadoes, the presence of filarial disease, which at present is quite alarming, could easily, with little trouble and expense, be greatly diminished, and thus save much suffering, as well as loss of time, hideous deformity, and doubtless in not a few instances loss of life."

XI

PARASITIC DISEASES

THE foregoing chapters were concerned with bacteriology alone, and with those curative or preventive methods of treatment that have come out of inoculation-experiments on animals. The lives that are saved, or safeguarded, by these methods, even in one year, must be many thousands in each country of the civilised world. And, beside human lives, there is the protection of sheep and cattle against anthrax, swine against rouget, horses against tetanus, cattle against rinderpest. In Cape Colony alone, so far back as 1899, about half a million cattle had received preventive treatment against rinderpest; and the sum total of human and animal lives saved or safeguarded, in all parts of the world, must be several millions by this time.

This and the next two chapters are concerned with methods that have come out of experiments on animals, but not out of bacteriology.

It is plain that the grosser parasites of the human body, tapeworms and the like, could not be explained or understood without the help of

feeding-experiments on animals. By this method, and by this alone, their life-history was discovered. They were known to Aristotle and to Hippocrates; but nothing was understood about them. They were never studied, for this among other reasons, that men believed in spontaneous generation; and the presence of lower forms of life inside human bodies was attributed to the fault of the patient, or the work of the devil. Then, at last, Redi (1712), and Swammerdam (1752) in his *Bibel der Natur*, struck at the doctrine of spontaneous generation, saying that it did not apply to insects; and in 1781 Pallas boldly declared that the internal parasites of man came out of eggs, like insects, and not "of themselves." It would be a good theme for an essay—*The paralysing effect, on medicine and surgery, of the doctrine of spontaneous generation.* Rudolphi (1808) and Bremser (1819) opposed Pallas; and von Siebold (1835) and Eschricht (1837) supported him. Then came the great students of this part of biology—Cobbold, Busk, Davaine, van Beneden, Leuckart, Küchenmeister. In 1842, Steenstrup had discovered, in certain insects, the alternation of generations; in 1852, Küchenmeister proved that the generations of internal parasites are similarly alternate. By feeding carnivorous animals with "measly" meat, he produced tapeworms in them; and by feeding herbivorous animals with the ova of tapeworms, he made their muscles "measly."

The feeding of animals was the only possible way to understand the bewildering transformations

and transmigrations of the thirty or more entozoa to which flesh is heir. This chapter of pathology makes up in tragedy what it lacks in romance; for these animal parasites have killed whole hosts of people. Take, for instance, the *trichina spiralis*, a minute worm discovered in 1835 encysted in countless numbers in the muscles of the human body; it was studied by Virchow, Leuckart, and others, by feeding-experiments on animals, and was proved to come from infected half-cooked ham and pork, and to make its way from the alimentary canal all over the body. The name of trichiniasis or trichina-fever was given to the acute illness that came of the sudden dissemination of these myriad parasites into the tissues. Trichiniasis had killed hundreds of people by a most painful death; outbreaks of it, in Germany and elsewhere, had swept through villages like cholera or plague: then Leuckart and Virchow traced it to its source, and it was stopped there—*Above all things, we must shut off the sources of the infection*—the butcher's shops were kept under sanitary inspection, people were warned against half-cooked ham and pork, and there was an end of it.

Or take hydatid disease, which occurs in all parts of the world, and in some countries (Australia, Iceland) is terribly common. The nature of this disease—that it is an animal parasite transmissible between men and dogs—was proved by feeding-experiments on animals. In Iceland, where men and dogs live crowded together in huts, there is

an appalling number of deaths from hydatid disease; Leuckart, in 1863, said of it:—

"At present, almost the sixth part of all the inhabitants annually dying in Iceland fall victims to the echinococcus epidemic."

Before Küchenmeister's experiments in 1852, there was no general knowledge of the exact pathology of entozoic disease. The advance was not made by the experimental method alone; other things helped: but among them were neither clinical experience, nor what Sir Charles Bell called "the observation of the just facts of anatomy and of natural motions."

Beside the entozoa, there are also vegetable parasites. Of these, the most important is the *streptothrix actinomyces*, the cause of actinomycosis in man and cattle. Israel, in 1877, gave the first accurate account of it in man; and Böllinger, the same year, studied it in cattle. Ponfick, in 1882, recognised the identity of the disease in man and animals. In 1885, Israel published the collected records of 37 cases in man, tabulated according to the site of the primary infection. Boström, about this time, made cultures of the fungus: but all the earlier attempts at inoculation failed; and it was not till 1891 that Wolff and Israel published their successful inoculations, and thus completed the evidence that actinomycosis is a parasitic infection, a growth of vegetable threads and spores,

transmissible between men and animals, and able to keep its vitality outside its host; so that men who are employed with cattle, or have the habit of chewing straws or ears of corn, incur some slight risk of infection. Before 1877, the disease was hardly suspected in man, and was not understood in cattle.

XII

MYXŒDEMA

ON 4th October 1873, Sir William Gull read a short paper before the Clinical Society of London, "On a Cretinoid State supervening in Adult Life in Women." This famous first account of myxœdema was based on five cases: it is less than five pages long, it does not suggest a name for the disease, and it says nothing about the thyroid gland. Four years later (23rd October 1877) Dr Ord read a paper before the Medico-Chirurgical Society of London, "On Myxœdema; a term proposed to be applied to an essential condition in the 'Cretinoid' Affection occasionally observed in Middle-aged Women." His work had begun so far back as 1861; and in this 1877 paper he gave not only clinical observations, but also pathological and chemical facts; and he noted, as one among many changes, wasting of the thyroid gland. He also pointed out the close resemblance between cases of myxœdema and cases of sporadic cretinism.

In 1882, Reverdin stated before the Medical Society of Geneva that signs like those of myxœ-

dema had been observed in some cases of removal of the thyroid gland on account of disease (goître). In April 1883, Kocher of Berne read a paper on this subject, before the Congress of German Surgeons; but he attributed this myxœdema after removal of the gland (cachexia strumipriva) not directly to the loss of thyroid-tissue, but rather to some sort of interference with free respiration, due to operation. On 23rd November, Sir Felix Semon brought the subject again before the Clinical Society; and on 14th December 1883, the Society appointed a Committee of Investigation to study the whole question.

Their report, 215 pages long, with tabulated records of 119 cases of myxœdema, was published in 1888. It is a monument of good work, historical, clinical, pathological, chemical, and experimental. Twenty years ago, the purpose of the thyroid gland was unknown: a few experiments had been made on it, by Sir Astley Cooper and others, and had failed; and Claude Bernard, in his *Physiologie Opératoire* (published in 1879, soon after his death), makes it clear that nothing was known in his time about it. He is emphasising the fact that anatomy cannot make the discoveries of physiology :—

"The descriptive anatomy, and the microscopic characters, of the thyroid gland, the facts about its blood-vessels and its lymphatics—are not all these as well known in the thyroid gland as in other organs? Is not the same thing true of the thymus gland, and the suprarenal capsules? *Yet we know absolutely nothing about the functions of*

these organs—we have not so much as an idea what use and importance they may possess — because experiments have told us nothing about them; and anatomy, left to itself, is absolutely silent on the subject."

Therefore, in 1882-83, things stood at this point—that the removal of a diseased thyroid gland had been followed, in some cases, by a train of symptoms such as Sir William Gull had recorded in 1873. Would the same symptoms follow removal of the healthy gland? The answer was given by Sir V. Horsley's experiments, begun in 1884. He was able, by removal of the gland, to produce in monkeys a chronic myxœdema, a cretinoid state, the facsimile of the disease in man: the same symptoms, course, tissue-changes, the same physical and mental hebetude, the same alterations of the excretions, the temperature, and the voice. It was now past doubt that myxœdema was due to want of thyroid-tissue, and to that alone; and that "cachexia strumipriva" was due to the loss, by operation, of such remnants of the gland as had not been rendered useless by disease.

The advance had still to be made from pathology to treatment. Here, so far as England is concerned, honour is again due to Sir V. Horsley. On 8th February 1890, he published the suggestion that thyroid-tissue, from an animal just killed, should be transplanted beneath the skin of a myxœdematous patient:—

"The justification of this procedure rested on

the remarkable experiments of Schiff and von Eisselsberg. I only became aware in April 1890, that this proposal had been in fact forestalled in 1889 by Dr Bircher, in Aarau. (The date of Dr Bircher's operation was 16th January 1889.) Kocher had tried to do the same thing in 1883, but the graft was soon absorbed; but early in 1889 he tried it again, in five cases, and one greatly improved."

The importance of this treatment, by transplantation of living thyroid-tissue, must be judged by the fact that in 1888 no practical use had yet been made of the scientific work that had been done. The Clinical Society's Report, published that year, give but half a page to treatment, of the old-fashioned sort; and not a word of hope.

Then, at last, in 1891, came Dr George Murray's paper in the *British Medical Journal*, "Note on the Treatment of Myxœdema by Hypodermic Injections of an Extract of the Thyroid Gland of a Sheep." Later, hypodermic injections of thyroid-extract gave way to sandwiches made with thyroid-gland (Dr Hector Mackenzie, and Dr Fox of Plymouth), and these in their turn were eclipsed by tabloids.*

It is a strange sequence, from 1873 onward: clinical observation, *post-mortem* work, calamities of surgery, experimental physiology, transplantation, hypodermic injections, sandwiches, and tabloids.

* It remains only to isolate, even more perfectly, the active principle or principles of thyroid-tissue: Blum's "thyreo-iodin" is perhaps a step in this direction.

And far more has been achieved than the cure of myxœdema. Even if the discovery stopped here, it would still be a miracle that little bottles of tabloids should bring men and women back from myxœdema to what they were before they became thick-witted, slow, changed almost past recognition, drifting toward idiocy. But it does not stop here. The same treatment has given good results in countless cases of sporadic cretinism, restoring growth of body and of mind to children that were hopelessly imbecile. It is of great value also for certain diseases of the skin. Moreover, physiology has gained knowledge of the purpose of the thyroid gland, and a clearer insight into the facts relating to internal secretion.

Myxœdema is but one instance how the treatment of disease must have the help of experiments on animals. Those who oppose all such experiments, now that they have faced or outfaced the facts about myxœdema, must face the facts about cancer. What do they wish to see done? They are absolutely ignorant of the elementary facts about the disease: will they advise the experts what line to follow?

XIII

THE ACTION OF DRUGS

LONG after the Renaissance, the practice of medicine was still under the influence of magic. Whatever things were rare and precious were held to be good against disease—gold, amber, coral, pearls, and the dust of mummies; whatever took strange forms of life—toads, earthworms, and the like; whatever looked like the disease, after the doctrine of signatures — pulmonaria for the lungs, because the spots on its leaves were like tubercle, a kidney-shaped fruit for the kidneys, a heart-shaped fruit for the heart, and yellow carrots for the yellow jaundice. Among the drugs in the 1618 Pharmacopœia are *cranium humanum*, *mandibula lucii*, *nidus hirundinum*, *sericum crudum*, *linum vivum*, and *pilus salamandræ*. In the Pharmacopœia of 1677 are *exuviæ serpentis*, *telæ arancarum*, *saliva jejuni*, *cranium hominis violentâ morte extincti*, and worse obscenities.

Soon after the publication of this Pharmacopœia, on 14th February 1685, King Charles II. died; and in the Library of the Society of Anti-

quaries there is a manuscript account in Latin, by Dr Scarbrugh, how the case was treated. The King had sixteen physicians, and nine consultations in five days; and to say "everything was done that was possible" gives no idea of the vigour of the treatment. Finally, the day he died, they gave him, eleven of them in consultation—*totus medicorum chorus ab omni spe destitutus*—they gave him, as *more generous cardiacs*, the *lapis Goæ*, and the *Bezoar-stone*. The *lapis Goæ* was a dust of topaz, jacinth, sapphire, ruby, pearl, emerald, bezoar, coral, musk, ambergris, and gold, all made into a pill and polished; and the *bezoar* is a calculus found in the intestines of herbivorous animals. Half a century later, the Pharmacopœia of 1721 still included ants' eggs, teeth, *lapis nephriticus*, and other horrors; and in the Pharmacopœia of 1746, though the dust of Egyptian mummies was ruled out, vipers and wood-lice were retained.

Certainly these "last enchantments of the Middle Ages" were slow to depart. Clinical observation, anatomy, and pathology, had all failed to bring about a right understanding of the actions of drugs. It was the physiologists, not the doctors, who first formulated the exact use of drugs; it was Bichat, Magendie, and Claude Bernard. That is the whole meaning of Magendie's work on the upas-poison and on strychnine, and Claude Bernard's work on curari and digitalis. Of these four substances, two only are of any use in practice; yet Magendie's study

of strychnine * was of immeasurable value, not so much because it gave the doctors a "more generous cardiac," though that was a great gift, but because it revealed the *selective* action of drugs. Contrast his account of strychnine with Ambroise Parè's story how they tested the bezoar-stone on the thief instead of hanging him; contrast Bernard's chapter on curari with Dr Scarbrugh's notes on the King's death, with all the Crown jewels inside him: you are in two different worlds. The *selective* action of drugs—the affinity between strychnine and the central nerve-cells, between curari and the terminal filaments of the motor nerves — that was the revolutionary teaching of science: and it çame, not by experience, but by experiment.

Take Professor Fraser's address on "The Action of Remedies, and the Experimental Method," at the International Medical Congress in London, 1881:—

"The introduction of this method is due to Bichat; and, by its subsequent application by Magendie, pharmacology was originated as the science we now recognise. Bichat represents a transition state, in which metaphysical conceptions were mingled with the results of experience. Magendie more clearly recognised the danger of adopting theories, in the existing imperfections of knowledge; and devoted himself to the supplementing of these imperfections by experiments on living

* For a full statement of the great value of this study of strychnine, see Cl. Bernard, *Leçons de Physiologie Opératoire*, 1879, p. 89.

animals. The advantages of such experiments he early illustrated by his investigation on the upas-poison; and afterwards by a research on the then newly discovered alkaloid, strychnia. . . . He demonstrated the action of this substance upon the spinal cord, by experiments upon the lower animals, so thoroughly, that subsequent investigations have added but little to his results."

Or take Professor Fraser's account of digitalis:—

"It was introduced as a remedy for dropsy; and, on the applications which were made of it for the treatment of that disease, a slowing action upon the cardiac movements was observed, which led to its acquiring the reputation of a cardiac sedative. Numerous observations were made on man by the originators of its application, by Dr Sanders and many other physicians, in which special attention was paid to its effects upon the circulation; but no further light was thrown upon its remarkable properties, with the unimportant exception that in some cases it was found to excite the circulation. It was not until the experimental method was applied in its investigation, in the first instance by Claude Bernard, and subsequently by Dybkowsky, Pelikan, Meyer, Boehm, and Schmiedeberg, that the true action of digitalis upon the circulation was discovered. It was shown that the effects upon the circulation were not in any exact sense sedative, but, on the contrary, stimulant and tonic, rendering the action of the heart more powerful, and increasing the tension in the blood-vessels. The indications for its use in disease were thereby revolutionised, and at the same time rendered more

exact; and the striking benefits which are now afforded by the use of this substance in most (cardiac) diseases were made available to humanity."

Or take Sir T. Lauder Brunton's account of the action of nitrite of amyl in angina pectoris:—

"The action of nitrite of amyl in causing flushing was first observed by Guthrie, and Sir B. W. Richardson recommended it as a remedy in spasmodic conditions, from the power he thought it to possess of paralysing motor nerves. In the spring of 1867 I had opportunities of constantly observing a patient who suffered from angina pectoris, and of obtaining from him numerous sphygmographic tracings, both during the attack and during the interval. These showed that during the attack the pulse became quicker, the blood-pressure rose, and the arterioles contracted. . . . It seemed probable that the great rise in tension was the cause of the pain, and it occurred to me that if it was possible to diminish the tension by drugs instead of by bleeding, the pain would be removed.

"I knew from unpublished experiments on animals by Dr A. Gamgee that nitrite of amyl had this power, and therefore tried it on the patient. My expectations were perfectly answered. The pain usually disappeared in three-quarters of a minute after the inhalation began, and at the same time the pulse became slower and much fuller, and the tension diminished."

Of course it would be easy to lengthen out the list. Aconite, belladonna, calcium chloride, colchicum, cocain, chloral, ergot, morphia, salicylic acid,

strophanthus, the chief diuretics, the chief diaphoretics—all these drugs, and a host more, have been studied and learned by experiments on animals. Then comes the answer, that drugs act differently on animals and on men. The few instances, that give a wise air to this foolish answer, were known long ago to everybody: they do not so much as touch the facts of daily practice:—

"The action of drugs on man differs from that on the lower animals chiefly in respect to the brain, which is so much more greatly developed in man. Where the structure of an organ or tissue is nearly the same in man and in the lower animals, the action of drugs upon it is similar. Thus we find that carbonic oxide, and nitrites, produce similar changes in the blood of frogs, dogs, and man, that curare paralyses the motor nerves, alike in them all, and veratria exerts upon the muscles of each its peculiar stimulant and paralysing action. Where differences exist in the structure of the various organs, we find, as we would naturally expect, differences in their reaction to drugs. Thus the heart of the frog is simpler than that of dogs or men, and less affected by the central nervous system; we consequently find that while such a drug as digitalis has a somewhat similar action upon the hearts of frogs, dogs, and men, there are certain differences between its effect upon the heart of a frog and on that of mammals.

"Belladonna offers another example of apparent difference in action—a considerable dose of belladonna will produce almost no apparent effect upon a rabbit, while a smaller dose in a dog or a man would cause the rapidity of the pulse to be nearly

doubled. Yet in all three—rabbits, dogs, and men —belladonna paralyses the power of the vagus over the heart. The difference is that in rabbits the vagus normally exerts but little action on the heart, and the effect of its paralysis is consequently slight or hardly appreciable." (Professor Fraser.)

It would be strange indeed, if experts who work in micromillimetres and decimal milligrammes, and study the vanishing-point of microscopic structures, and measure and ordain infinitesimal changes in invisible organisms, were blind to such gross and palpable differences as exist between men and pigeons in their susceptibility to a dose of opium.

Anæsthetics must be reckoned among the drugs that have been studied on animals: but, for the discovery of them, men experimented on themselves. The first use of nitrous oxide (laughing gas) in surgery was 11th December 1844, when Horace Wells, of Connecticut, had it administered to himself for the removal of a tooth. The first use of ether was made by Dr Long, of Athens, Georgia; but he did not publish the case, or follow up the work: and the honour of the discovery of ether went to Morton, of Boston, who made repeated experiments, both on animals and on himself. The date when he first rendered himself absolutely unconscious for seven or eight minutes, is 30th September 1846; and the first operation under ether was done on 16th October, in the Massachusetts General Hospital. The first use of chloroform was 4th November 1847, that famous evening when Simpson, George Keith, and Matthews Duncan took it together. The whole

history of anæsthesia is to be found in the *Practitioner*, October 1896.

It is sometimes said that the men who make experiments on animals ought to make them on themselves. But they do, hundreds of them, and suffer for it: Heaven knows the list is long enough —the discoverers of anæthesia, Hunter, Garré, Koch, Klein, Moor, Haffkine, Grassi, Bochefontaine, Quesada, Sanarelli, Pettenkofer—these and many more, here or abroad, have done it, as part of the day's work; and some—by accidental infection, like Chabry and Villa, or by deliberate self-inoculation, like Carrion—have been killed:—

"Dr Angelo Knorr, *Privat-docent* in the Veterinary School of Munich, died on 22nd February from acute glanders, contracted in the course of an experimental research on mallein. Helmann, the Russian investigator who discovered mallein, himself fell a victim to accidental inoculation of the glanders virus. Some time afterwards another Russian, Protopopow, died of glanders contracted in a French laboratory. An Austrian physician, Dr Koffman-Wellenhof, died of the same disease, contracted in the Institute of Hygiene at Vienna. On 17th January of the present year Dr Guiseppe Bosso, of the University of Turin, died of infection contracted in the course of cultivations of tubercle-bacilli made in his laboratory. Not long before, Dr Lola, assistant in the maternity department of the Czech University Hospital of Prague, died of tetanus caused by an experimental inoculation made on himself. Some fourteen or fifteen years ago, a medical student of Lima proved that 'verruga Peruana' is an infectious disease by inoculating

himself with it, an act of scientific devotion which cost him his life.* Besides those who have died, there are many who have only escaped with their lives after long and painful illness. Professor Kourloff contracted anthrax in a laboratory at Munich, and was saved only by vigoroùs surgery. Dr Nicolas supplied, in his own person, the first example of tetanus produced in man by inoculation of the pure toxin of the bacillus of Nicolaier." (*Brit. Med. Journal*, 18th March 1899.)

This list is three years old now; it is twice the length by this time. Typhoid, malaria, yellow fever, have all taken toll of those who study them. It is a long record of the men who fell ill, or died, or killed themselves over their work; and the deaths of Barisch, Dr Müller, and Nurse Pecha, from plague at Vienna (October 1898) are another instance that there is danger in the constant handling of cultures. But these deaths at Vienna were due to the great carelessness of one man. In laboratories in all parts of the world there are stored cultures of all sorts of organisms, yet no harm comes of it. "More cases of infection occur amongst young medical men attending fever cases, whether in private practice or hospital wards, in a single month, than have occurred in the whole of the laboratories in the world since they were established." (*British Medical Journal*, 29th

* Daniel Carrion, born 1859 at Cerro de Pasco, proved, by self-inoculation, the identity of the two forms of the disease, 27th August 1885; died of the disease, 5th October. See *Ann. de l'Inst. Past.*, Sept. 1898.

October 1898.) Outside the laboratory, outside the fever hospitals, the risk is something less than a negligible quantity:—

"Apart from plague and cholera, in all the big laboratories studies are uninterruptedly pursued, from one end of the year to the other, upon anthrax, glanders, influenza, Malta fever, various tropical diseases which do not exist at all or are rare in the countries where they are being studied. The laboratories in question are situated in the largest and most important towns of their respective countries; and, within those towns, very often in the most fashionable or most populous centres. . . . On no occasion was there even a suspicion aroused of an epidemic having been produced by any of the above-mentioned institutes, or by those tens of thousands of operations against cholera performed in India." (Haffkine, *Madras Mail*, 8th December 1898.)

XIV

SNAKE-VENOM

THE Report of the 1875 Commission said :—

"It is not possible for us to recommend that the Indian Government should be prohibited from pursuing its endeavours to discover an antidote for snake-bites; or that, without such an effort, your Majesty's Indian subjects should be left to perish in large numbers annually from the effects of these poisons."

Certainly it was not possible; and the numbers are large indeed. During 1897, 4227 persons were killed by wild animals in India, and 20,959 by snakes. (*British Medical Journal*, 5th November 1898.)

Sir Joseph Fayrer's name must be put in the highest place of all those who have studied the venomous snakes of India.

Sewell, in 1887, showed that animals could be rendered immune, by repeated inoculation with minute quantities of rattlesnake-venom, to a dose seven times as large as would kill an unprotected animal. Kanthack, in 1891, immunised animals in

the same way against cobra-venom. He also made experiments to ascertain whether the blood-serum of these animals acted as an antidote to the venom. Then came the work of Calmette, Fraser, Phisalix, Bertrand, Martin (Australia), Stephens, and Meyers. Professor Fraser's observations on the antidotal properties of the bile are, of course, of the utmost importance; not only in preventive medicine, but also in physiology. The results obtained by Calmette are a good instance of the fineness and accuracy of the experimental method. It is to be noted that the animals were inoculated with a fine needle, not thrust into cages with snakes, as at zoological gardens; and that an animal thus poisoned has a painless death. The different venoms were measured in decimal milligrammes, and their potency was estimated according to the body-weight of the animal inoculated. As with tetanus, so with snake-venom, there must be a standard, or "unit of toxicity":—

"The following table gives the relative toxicity, for 1 kilogr. of rabbit, of the different venoms that I have tested. To denote this toxicity I use terms such as Behring, Roux, and Vaillard used for the toxin of tetanus, taking the number of grammes of animal killed by one gramme of toxin:—

1. Venom of *naja*.....0.25 mgr. per kilogr. of rabbit. One gramme of this venom kills 4000 kilogrammes of rabbit; it has, therefore, an activity of..... 4,000,000
2. Venom of *hoplocephalus*.....0.29 mgr. ... 3,450,000
3. Venom of *pseudechis*.....1.25 mgr. ... 800,000
4. Venom of *pelias berus*.....4.00 mgr. ... 250,000

"Of course, this estimation of virulence is not absolute; it varies considerably according to the species of animal tested. Thus the guinea-pig, and still more the rat, are extremely sensitive. For instance, 0.15 mgr. of viper-venom is enough to kill, in less than 12 hours, 500 grammes of guinea-pig; so that the activity of this venom with a guinea-pig is 3,333,000, but with a rabbit is not more than 650,000. With more resistent animals, the opposite result is obtained; about 10 mgr. of cobra-venom are necessary to kill a dog of 6.50 kilogrm. weight; but to kill the same weight of rabbit 1.65 mgr. is enough. Thus the virulence of this venom with the rabbit is 4,000,000; but with the dog not more than 650,000."

By experiments in test-tubes, Calmette studied these venoms under the influences of heat and various chemical agents. He found how to attenuate their virulence, and how to diminish the local inflammation round the point of inoculation; and it was in the course of these test-tube experiments and inoculations that he discovered the value of calcium hypochlorite as a local application. Working, by various methods, with attenuated venoms, he was able to immunise animals:—

"I have come to immunise rabbits against quantities of venom that are truly colossal. I have got several, vaccinated more than a year ago, which take, without the least discomfort, so much as 40 mgr. of venom of *naja tripudians* at a single injection; that is to say, enough to kill 80 rabbits of 2 kilogr. weight, or 5 dogs.

"Five drops of serum from these rabbits wholly

neutralise *in vitro* (in a glass test-tube) the toxicity of 1 mgr. of *naja*-venom."

By 1894 he had found that the serum of an animal, thus immunised by graduated doses of one kind of venom, neutralised other kinds of venom:—

"If 1 mgr. of cobra-venom, or 4 mgr. of viper-venom, be mixed, in a test-tube, with a small quantity of serum from an immunised rabbit, and a fresh rabbit be inoculated with this mixture, it does not suffer any discomfort. It is not even necessary that the serum should come from an animal vaccinated against the same sort of venom as that in the mixture. *The serum of a rabbit immunised against the venom of the cobra or the viper acts indifferently on all the venoms that I have tested.*"

In 1894 he had prepared enough serum for the treatment to be tried by his own countrymen practising in some of the French colonies. In April 1895, he gave the following account of his work:—

"I have immunised two asses, one having received 220 mgr. of *naja*-venom from 25th September to 31st December 1894, and the other 160 mgr. from 15th October to 31st December. The serum of the first of these two animals has now reached this point, that half a cubic centimetre destroys the toxicity of 1 mgr. of *naja*-venom. Four cubic centimetres of this serum, injected four hours before the inoculation of a dose of venom enough to kill twice over, preserve the animal in every case. It

is also therapeutic, under the conditions that I have already defined; that is to say, if you first inoculate a rabbit with such a dose of venom as kills the control-animals in three hours, and then, an hour after injecting the venom, inject under the skin of the abdomen 4 to 5 cubic centimetres of serum, recovery is the rule. When you interfere later than this the results are uncertain; and in all my experiments the delay of an hour and a half is the most that I have been able to reach.

"This antivenomous serum of asses has these same antitoxic properties with all kinds of snake-venom; it is equally active *in vitro*, preventive, and therapeutic, with the venoms of *cerastes*, of *trigonocephalus*, of *crotalus*, and of four kinds of Australian snakes that Mr MacGarvie Smith has sent to M. Roux. I am still injecting these two animals with venom, and I hope to give to their serum at last a much greater antitoxic power.

In 1896 four successful cases of this treatment in the human subject were reported in the *British Medical Journal*. In 1898 Calmette made the following statement of his results:—

"It is now nearly two years since the use of my antivenomous serum was introduced in India, in Algeria, in Egypt, on the West Coast of Africa, in America, in the West Indies, Antilles, etc. It has been very often used for men and domestic animals (dogs, horses, oxen), and up to now none of those that have received an injection of serum have succumbed. . . . A great number of observations have been communicated to me, and not one of them refers to a case of failure." (*British Medical Journal*, 14th May 1898.)

Good accounts of Fraser's and Calmette's work are given by Dr Stone in the *Boston Medical and Surgical Journal*, 7th April 1898, and by Staff-Surgeon Andrews, R.N., in the *British Medical Journal*, 9th September 1899. For other cases, see the *Pioneer*, 10th August 1899, the *Lancet*, 25th November 1899, and the *British Medical Journal*, 23rd December 1899. In one of these cases, recorded by Dr Rennie, the patient was, literally, at the point of death, but recovered after the serum had been injected. Two cases have also been recorded of cobra-bite during work in the laboratory: both of them recovered after injection. "Every Government or private dispensary," says Surgeon Beveridge, "should be supplied with antivenene, which is certainly the best remedy for snake-bite available." The cases are few at present; but it does not appear that the treatment has failed in any case; and, with a new remedy of this kind, it is fairly certain that failures would be published.

From all these instances in physiology, pathology, bacteriology, and therapeutics, we come to consider the Act relating to experiments on animals in the United Kingdom. Many subjects have been left out; among them, the work of the last few years on the suprarenal glands and adrenalin, and Dr William Hunter's admirable work on pernicious anæmia. Nothing has been said about those discoveries in bacteriology that have not yet

been applied to practice; and nothing has been said of the many inventions of medical and surgical practice that owe only an indirect debt to experiments on animals. Artificial respiration, the transfusion of saline fluid, the hypodermic administration of drugs, the use of oxygen for inhalation, the torsion of arteries, the grafting of skin, the transplantation of bone, the absorbable ligature, the diagnostic and therapeutic uses of electricity, the rational employment of blood-letting —all these good methods have been left out of the list; only some facts have been presented, those that mark most clearly the advance of knowledge and of practice, and stand up even above the rest of the work. There they will stand, when we are all dead and gone: and by them, as by landmarks, all further advance will be guided.

PART III

THE ACT RELATING TO EXPERIMENTS ON ANIMALS IN GREAT BRITAIN AND IRELAND

ACT 39 AND 40 VIC. C. 77

THE Royal Commission "On the Practice of subjecting Live Animals to Experiments for Scientific Purposes," was appointed on 22nd June 1875. Its members were—Lord Cardwell (chairman), Lord Winmarleigh, Mr W. E. Forster, Sir John Karslake, Mr Huxley, Mr (Sir John) Erichsen, and Mr Hutton. Between 5th July and 30th December, 53 witnesses were examined, and 6551 questions were put and answered. The report of the Commission bears date 8th January 1876, and in that year the present Act received the Royal Assent.

The evidence before the Commission was all, or nearly all, concerned with physiology, with the work of Magendie, Claude Bernard, and Sir Charles Bell, the action of curare, the *Handbook of the Physiological Laboratory*, the teaching of physiology, and so forth. Very little was said of pathology; and, of bacteriology, next to nothing. Practically, physiology alone came before the Commissioners; and such experiments in physiology as are now, the youngest of them, more than a quarter of a century old.

Bacteriology, at the time of the passing of

the Act, had hardly made a beginning. Therefore the Act made no special provision for inoculations, injections, and the whole study of immunisation of animals and men against disease. Experiments of this kind have to be scheduled under one of the existing certificates, to bring them under an Act that was drafted without foreknowledge of them. Certificate A or Certificate B has to be used for this purpose:—

Certificate A.

"We hereby certify that, in our opinion, insensibility in the animal on which any such experiment may be performed cannot be produced by anæsthetics without necessarily frustrating the object of such experiment."

Certificate B.

"We hereby certify that, in our opinion, the killing of the animal on which any such experiment is performed before it recovers from the influence of the anæsthetic administered to it, would necessarily frustrate the object of such experiment."

Under one or other of these certificates must be scheduled all inoculations, injections, feeding-experiments, transplantations of particles of disease, immunisations, and the like. They must be scheduled somehow; and that is the only way of doing it. Where the act of inducing the disease would itself give any pain, if an anæsthetic were not administered—as in the subdural inoculation of

a rabbit, or the intra-peritoneal inoculation of an animal with a particle of cancerous tissue—there the licensee must hold, together with his license, Certificate B, because the act of inducing the disease is itself an operation, done under an anæsthetic. If the animal be a dog or a cat, he must hold Certificates B and EE; if it be a horse, ass, or mule, Certificates B and F.

Where the act of inducing the disease is not itself painful—as in ordinary inoculation, and in feeding-experiments — the licensee must hold, together with his license, Certificate A, because the animal is not anæsthetised. It is not a painful operation; the experiment consists not in the act of putting the hypodermic needle under the animal's skin, but in the subsequent observation of the course of the disease. Take, for instance, the inoculation of a guinea-pig with tubercle-bacilli: the experiment is the production of tubercle; the experiment lasts till the animal is killed and found to be infected; it is therefore scheduled under Certificate A. Or take the testing, on an animal, of an antitoxin; the experiment is not the injection, but the observation of the result; the animal may not suffer, but the injection must still be done under Certificate A. And, if the animal be a dog or a cat, the licensee must hold Certificates A and E; or, if it be a horse, ass, or mule, Certificates A and F.

This want of a special certificate for inoculations is an important matter, because it has led to the belief that painful operations are performed,

without anæsthesia, in cases where the only instrument used is a needle. It is hardly reasonable, for instance, that the inoculation of a mouse should be scheduled as a painful operation performed without anæsthesia. The disease, thus painlessly induced, may in many cases be called painless; for instance, snake-venom in the rat, septicæmia in the mouse, malaria in small birds. In other cases, there are such pain and fever as are part of the disease. The form that rabies take in rabbits may fairly be called painless. Inoculations not under the skin, but into the anterior chamber of the eye, are very seldom made; they sound cruel, but cocain renders the surface of the eye wholly insensitive, and the anterior chamber is so far insensitive that a man with blood or pus (*hypopyon*) in the anterior chamber of the eye may suffer no pain from it. A horse or an ass kept for the giving of an antitoxic serum has a more comfortable life than an omnibus horse; and this preparation of the antitoxins, since it is not an experiment, but a direct use of animals in the recognised service of man, does not require a license or certificates under the Act. But the testing of an antitoxin is an experiment, and must be made under a license and Certificate A.

It is not the business of this book to consider whether the sensitiveness of a dog, a rabbit, or a guinea-pig can fairly be stated in terms of the physical and mental sensitiveness of men and women. In the world of animals, as in the world of humanity, there are differences of sensitiveness.

Anyhow, the pain inflicted on animals may in some cases be measured :—

"A guinea-pig that will rest quietly in your hands before you commence to inject it, will remain perfectly quiet during the introduction of the needle under the skin; and the moment it is returned to the cage it resumes its interrupted feeding.

"Arteries, veins, and most of the parts of the viscera are in the same way (as the heart) * without the sense of touch. We have actual proof of this in what takes place when a horse is bled for the purpose of obtaining curative serum. With a sharp lance a cut may be made in the skin so quickly and easily that the animal does nothing more than twitch the skin-muscle of the neck, or give his head a shake, whilst of the further proceeding of introducing a hollow needle into the vein the animal takes not the slightest notice. Some horses, indeed, will stand perfectly quiet during the whole operation, munching a carrot, nibbling at a wisp of hay, or playing with a button on the vest of the groom standing at its head.

"Harrowing details concerning the horrors of trephining rabbits for Pasteur's antirabic treatment are frequently supplied for popular consumption, but how little real existence any suffering in connection with the operation has, may be gathered from the fact that if, as a preliminary measure, the skin be benumbed with carbolic acid, the whole operation, from making the incision through the

* The reference is to the famous case showed by Harvey to King Charles I., where the heart was exposed almost naked through an opening in the chest, and was found insensitive. See Power's *Life of Harvey*, p. 246.

skin to cutting out the piece of bone with a fine trephine and passing a needle under the dura mater, may be done without once causing the animal to withdraw its attention from the important business of munching a bit of cabbage-leaf or a scrap of succulent carrot." (Woodhead, *Medical Magazine*, June 1898.)

It may be well put here—(1) the full text of the Act, and of the License and Certificates granted in accordance with the Act; (2) an account of the anæsthetics used for animals; (3) the Reports of Government Inspectors appointed under the Act, for the last three years, 1899 to 1901.

I.—An Act to amend the Law relating to Cruelty to Animals.

15th August 1876.

A.D. 1876.

Whereas it is expedient to amend the law relating to cruelty to animals by extending it to the cases of animals which for medical, physiological, or other scientific purposes are subjected when alive to experiments calculated to inflict pain:

Be it enacted by the Queen's most Excellent Majesty, by and with the advice and consent of the Lords Spiritual and Temporal, and Commons, in this present Parliament assembled, and by the authority of the same, as follows:

Short title.

1. This Act may be cited for all purposes as "The Cruelty to Animals Act, 1876."

Prohibition of painful experiments on animals.

2. A person shall not perform on a living animal any experiment calculated to give pain, except subject to the restrictions imposed by this Act. Any person performing or taking part in performing any experiment calculated to give pain, in contravention of this Act, shall be guilty of an offence

against this Act, and shall, if it be the first offence, be liable to a penalty not exceeding fifty pounds, and if it be the second or any subsequent offence, be liable, at the discretion of the court by which he is tried, to a penalty not exceeding one hundred pounds, or to imprisonment for a period not exceeding three months. A.D. 1876.

General restrictions as to performance of painful experiments on animals.

3. The following restrictions are imposed by this Act with respect to the performance on any living animal of an experiment calculated to give pain; that is to say,

(1.) The experiment must be performed with a view to the advancement by new discovery of physiological knowledge or of knowledge which will be useful for saving or prolonging life or alleviating suffering; and

(2.) The experiment must be performed by a person holding such license from one of Her Majesty's Principal Secretaries of State, in this Act referred to as the Secretary of State, as is in this Act mentioned, and in the case of a person holding such conditional license as is hereinafter mentioned, or of experiments performed for the purpose of instruction in a registered place; and

(3.) The animal must, during the whole of the experiment, be under the influence of some anæsthetic of sufficient power to prevent the animal feeling pain; and

(4.) The animal must, if the pain is likely to continue after the effect of the anæsthetic has ceased, or if any serious injury has been inflicted on the animal, be killed before it recovers from the influence of the anæsthetic which has been administered; and

(5.) The experiment shall not be performed as an illustration of lectures in medical schools, hospitals, colleges, or elsewhere; and

(6.) The experiment shall not be performed for the purpose of attaining manual skill.

A.D. 1876.

Provided as follows; that is to say,

(1.) Experiments may be performed under the foregoing provisions as to the use of anæsthetics by a person giving illustrations of lectures in medical schools, hospitals, or colleges, or elsewhere, on such certificate being given as in this Act mentioned, that the proposed experiments are absolutely necessary for the due instruction of the persons to whom such lectures are given with a view to their acquiring physiological knowledge, or knowledge which will be useful to them for saving or prolonging life, or alleviating suffering; and

(2.) Experiments may be performed without anæsthetics on such certificate being given as in this Act mentioned, that insensibility cannot be produced without necessarily frustrating the object of such experiments; and

(3.) Experiments may be performed without the person who performed such experiments being under an obligation to cause the animal, on which any such experiment is performed, to be killed before it recovers from the influence of the anæsthetic on such certificate being given as in this Act mentioned, that the so killing the animal would necessarily frustrate the object of the experiment, and provided that the animal be killed as soon as such object has been attained; and

(4.) Experiments may be performed not directly for the advancement by new discovery of physiological knowledge, or of knowledge which will be useful for saving or prolonging life, or alleviating suffering, but for the purpose of testing a particular former discovery alleged to have been made for the advancement of such knowledge as last aforesaid, on such certificate being given as is in this Act mentioned that such testing is absolutely necessary for the effectual advancement of such knowledge.

4. The substance known as urari or curare shall not for the purposes of this Act be deemed to be an anæsthetic.

Use of urari as an anæsthetic prohibited.

5. Notwithstanding anything in this Act contained, an experiment calculated to give pain shall not be performed without anæsthetics on a dog or cat, except on such certificate being given as in this Act mentioned, stating, in addition to the statements hereinbefore required to be made in such certificate, that for reasons specified in the certificate the object of the experiment will be necessarily frustrated unless it is performed on an animal similar in constitution and habits to a cat or dog, and no other animal is available for such experiment; and an experiment calculated to give pain shall not be performed on any horse, ass, or mule except on such certificate being given as in this Act mentioned that the object of the experiment will be necessarily frustrated unless it is performed on a horse, ass, or mule, and that no other animal is available for such experiment.

Special restrictions on painful experiments on dogs, cats, etc.

6. Any exhibition to the general public, whether admitted on payment of money or gratuitously, of experiments on living animals calculated to give pain shall be illegal.

Absolute prohibition of public exhibition of painful experiments.

Any person performing or aiding in performing such experiments shall be deemed to be guilty of an offence against this Act, and shall, if it be the first offence, be liable to a penalty not exceeding fifty pounds, and if it be the second or any subsequent offence, be liable, at the discretion of the court by which he is tried, to a penalty not exceeding one hundred pounds, or to imprisonment for a period not exceeding three months.

And any person publishing any notice of any such intended exhibition by advertisement in a newspaper, placard, or otherwise shall be liable to a penalty not exceeding one pound.

A person punished for an offence under this section shall not for the same offence be punishable under any other section of this Act.

Administration of Law.

Registry of place for performance of experiments.

7. The Secretary of State may insert, as a condition of granting any license, a provision in such license that the place in which any experiment is to be performed by the licensee is

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to be registered in such manner as the Secretary of State may from time to time by any general or special order direct; provided that every place for the performance of experiments for the purpose of instruction under this Act shall be approved by the Secretary of State, and shall be registered in such manner as he may from time to time by any general or special order direct.

License by Secretary of State.

8. The Secretary of State may license any person whom he may think qualified to hold a license to perform experiments under this Act. A license granted by him may be for such time as he may think fit, and may be revoked by him on his being satisfied that such license ought to be revoked. There may be annexed to such license any conditions which the Secretary of State may think expedient for the purpose of better carrying into effect the objects of this Act, but not inconsistent with the provisions thereof.

Reports to Secretary of State.

9. The Secretary of State may direct any person performing experiments under this Act from time to time to make such reports to him of the result of such experiments, in such form and with such details as he may require.

Inspection by Secretary of State.

10. The Secretary of State shall cause all registered places to be from time to time visited by inspectors for the purpose of securing a compliance with the provisions of this Act, and the Secretary of State may, with the assent of the Treasury as to number, appoint any special inspectors, or may from time to time assign the duties of any such inspectors to such officers in the employment of the Government, who may be willing to accept the same, as he may think fit, either permanently or temporarily.

Certificate of scientific bodies for exceptions to general regulations.

11. Any application for a license under this Act and a certificate given as in this Act mentioned must be signed by one or more of the following persons; that is to say,

The President of the Royal Society;

The President of the Royal Society of Edinburgh;

The President of Royal Irish Academy;

The Presidents of the Royal Colleges of Surgeons in London, Edinburgh, or Dublin;

The Presidents of the Royal Colleges of Physicians in London, Edinburgh, or Dublin;

The President of the General Medical Council;

The President of the Faculty of Physicians and Surgeons of Glasgow;

The President of the Royal College of Veterinary Surgeons, or the President of the Royal Veterinary College, London, but in the case only of an experiment to be performed under anæsthetics with a view to the advancement by new discovery of veterinary science;

and also (unless the applicant be a professor of physiology, medicine, anatomy, medical jurisprudence, materia medica, or surgery in a university in Great Britain or Ireland, or in University College, London, or in a college in Great Britain or Ireland, incorporated by royal charter) by a professor of physiology, medicine, anatomy, medical jurisprudence, materia medica, or surgery in a university in Great Britain or Ireland, or in University College, London, or in a college in Great Britain or Ireland, incorporated by royal charter.

Provided that where any person applying for a certificate under this Act is himself one of the persons authorised to sign such certificate, the signature of some other of such persons shall be substituted for the signature of the applicant.

A certificate under this section may be given for such time or for such series of experiments as the person or persons signing the certificate may think expedient.

A copy of any certificate under this section shall be forwarded by the applicant to the Secretary of State, but shall not be available until one week after a copy has been so forwarded.

The Secretary of State may at any time disallow or suspend any certificate given under this section.

Power of judge to grant license for experiment when necessary in criminal case.

12. The powers conferred by this Act of granting a license or giving a certificate for the performance of experiments on living animals may be exercised by an order in writing under the hand of any judge of the High Court of Justice in England, of the High Court of Session in Scotland, or of any of the superior courts in Ireland, including any court to which

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the jurisdiction of such last-mentioned courts may be transferred, in a case where such judge is satisfied that it is essential for the purposes of justice in a criminal case to make any such experiment.

Legal Proceedings.

Entry on warrant by justice.

13. A justice of the peace, on information on oath that there is reasonable ground to believe that experiments in contravention of this Act are being performed by an unlicensed person in any place not registered under this Act may issue his warrant authorising any officer or constable of police to enter and search such place, and to take the names and addresses of the persons found therein.

Any person who refuses admission on demand to a police officer or constable so authorised, or obstructs such officer or constable in the execution of his duty under this section, or who refuses on demand to disclose his name or address, or gives a false name or address, shall be liable to a penalty not exceeding five pounds.

Prosecution of offences and recovery of penalties in England.

14. In England, offences against this Act may be prosecuted and penalties under this Act recovered before a court of summary jurisdiction in manner directed by the Summary Jurisdiction Act.

In England "Summary Jurisdiction Act" means the Act of the session of the eleventh and twelfth years of the reign of Her present Majesty, chapter forty-three, intituled "An Act to facilitate the performance of "the duties of justices of the peace out of sessions "within England and Wales with respect to summary "convictions and orders," and any Act amending the same.

"Court of summary jurisdiction."

"Court of summary jurisdiction" means and includes any justice or justices of the peace, metropolitan police magistrate, stipendiary or other magistrate, or officer, by whatever name called, exercising jurisdiction in pursuance of the Summary Jurisdiction Act: Provided that the court when hearing and determining an information under this Act shall be constituted either

of two or more justices of the peace in petty sessions, sitting at a place appointed for holding petty sessions, or of some magistrate or officer sitting alone or with others at some court or other place appointed for the administration of justice, and for the time being empowered by law to do alone any act authorised to be done by more than one justice of the peace.

Power of offender in England to elect to be tried on indictment, and not by summary jurisdiction.

15. In England, where a person is accused before a court of summary jurisdiction of any offence against this Act in respect of which a penalty of more than five pounds can be imposed, the accused may, on appearing before the court of summary jurisdiction, declare that he objects to being tried for such offence by a court of summary jurisdiction, and thereupon the court of summary jurisdiction may deal with the case in all respects as if the accused were charged with an indictable offence and not an offence punishable on summary conviction, and the offence may be prosecuted on indictment accordingly.

Form of appeal to quarter sessions.

16. In England, if any party thinks himself aggrieved by any conviction made by a court of summary jurisdiction on determining any information under this Act, the party so aggrieved may appeal therefrom, subject to the conditions and regulations following :

(1.) The appeal shall be made to the next court of general or quarter sessions for the county or place in which the cause of appeal has arisen, holden not less than twenty-one days after the decision of the court from which the appeal is made ; and

(2.) The appellant shall, within ten days after the cause of appeal has arisen, give notice to the other party and to the court of summary jurisdiction of his intention to appeal, and of the ground thereof ; and

(3.) The appellant shall, within three days after such notice, enter into a recognizance before a justice of the peace, with two sufficient sureties, conditioned personally to try such appeal, and to abide the judgment of the court thereon, and to pay such costs as may be awarded by the court, or give such

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other security by deposit of money or otherwise as the justice may allow; and

(4.) Where the appellant is in custody the justice may, if he think fit, on the appellant entering into such recognizance or giving such other security as aforesaid, release him from custody; and

(5.) The court of appeal may adjourn the appeal, and upon the hearing thereof they may confirm, reverse, or modify the decision of the court of summary jurisdiction, or remit the matter to the court of summary jurisdiction with the opinion of the court of appeal thereon, or make such other order in the matter as the court thinks just, and if the matter be remitted to the court of summary jurisdiction the said last-mentioned court shall thereupon re-hear and decide the information in accordance with the order of the said court of appeal. The court of appeal may also make such order as to costs to be paid by either party as the court thinks just.

Prosecution of offences and recovery of penalties in Scotland.

17. In Scotland, offences against this Act may be prosecuted and penalties under this Act recovered under the provisions of the Summary Procedure Act, 1864, or if a person accused of any offence against this Act in respect of which a penalty of more than five pounds can be imposed, on appearing before a court of summary jurisdiction, declare that he objects to being tried for such offence in the court of summary jurisdiction, proceedings may be taken against him on indictment in the Court of Justiciary in Edinburgh or on circuit.

Every person found liable in any penalty or costs shall be liable in default of immediate payment to imprisonment for a term not exceeding three months, or until such penalty or costs are sooner paid.

Prosecution of offences and recovery of penalties in Ireland.

18. In Ireland, offences against this Act may be prosecuted and penalties under this Act recovered in a summary manner, subject and according to the provisions with respect to the prosecution of offences, the recovery of penalties, and to appeal of the Petty Sessions (Ireland) Act, 1851, and any Act amending the same, and in Dublin of the Acts regulating the powers

of justices of the peace or of the police of Dublin metropolis. All penalties recovered under this Act shall be applied in manner directed by the Fines (Ireland) Act, 1871, and any Act amending the same.

Power of offender in Ireland to elect to be tried on indictment, and not by summary jurisdiction.

19. In Ireland, where a person is accused before a court of summary jurisdiction of any offence against this Act in respect of which a penalty of more than five pounds can be imposed, the accused may, on appearing before the court of summary jurisdiction, declare that he objects to being tried for such offence by a court of summary jurisdiction, and thereupon the court of summary jurisdiction may deal with the case in all respects as if the accused were charged with an indictable offence and not an offence punishable on summary conviction, and the offence may be prosecuted on indictment accordingly.

Interpretation of "the Secretary of State" as to Ireland.

20. In the application of this Act to Ireland the term "the Secretary of State" shall be construed to mean the Chief Secretary to the Lord Lieutenant of Ireland for the time being.

Prosecution only with leave of Secretary of State.

21. A prosecution under this Act against a licensed person shall not be instituted except with the assent in writing of the Secretary of State.

Not to apply to invertebrate animals.

22. This Act shall not apply to invertebrate animals.

APPLICATION FOR LICENCE.

*Address*_____

*Date*_____

To the Right Honourable the Secretary of State for the Home Department.

SIR,

I*_____

* Here insert name and profession (see Sec. 11 of Act) of Applicant.

beg to apply under the above-mentioned Act for a Licence for the performance of experiments on animals.

† Here insert registered place. If the place is not registered, it will be necessary for the person having authority over the building to apply to the Secretary of State for its registration.

The place in which it is proposed that the experiments are to be performed is †_____

‡ Here insert a general description of proposed experiments and their object; also state, if that is the case, the intention of Applicant to send in a certificate or certificates (describing each certificate by its appropriate letter) with reference to the same experiments, or any other circumstances that may be material. See also Note at the end of the application.

The experiments which it is proposed to perform are ‡

APPLICATION FOR LICENCE—*Continued.*

This application is supported by the recommendations appearing below.

I am,

SIR,

Your obedient Servant,

*_____

* Here Applicant to sign his name.

We recommend that the above application be granted.

1. †_____

† Here the person recommending is to sign his name.

‡_____

‡ Here specify statutory qualification (see Sec. 11).

2. †_____

‡_____

N.B.—If the Licence is held alone without Certificate, the animal must be kept in anæsthesia throughout the whole of the experiment, and if the pain is likely to continue after the effect of the anæsthetic has ceased, or if any serious injury has been inflicted on the animal, it must be killed before the anæsthesia has passed off.

Certificate A dispenses altogether from the obligation to use an anæsthetic. It will be necessary in cases of simple inoculation calculated to give pain but not involving any surgical operation.

" B dispenses from the obligation to kill the animal before the anæsthesia has passed off; it is necessary therefore whenever the initial operation is to be done under anæsthetics, but the animal is to be allowed to survive.

" C is necessary for Experiments illustrating Lectures.

" E is never held alone, but is necessary whenever any experiment is to be performed on a Dog or Cat under Certificate A.

" EE is never held alone, but it is necessary whenever any experiment is to be performed on a Dog or Cat under Certificate B.

F is necessary whenever any experiment is to be performed on a Horse, Ass, or Mule.

CERTIFICATE A.

WHEREAS *

* Here insert name, address, and profession of person to whom Certificate is to be given. (Sec. 11 of Act.)

has represented to us †

† Here insert name, address, and statutory qualification of each person certifying. (Sec. 11 of Act.)

that he proposes, if duly authorized under the above-mentioned Act, to perform on living animals certain experiments described below: We hereby certify that, in our opinion, insensibility in the animal on which any such experiment may be performed cannot be produced by anæsthetics without necessarily frustrating the object of such experiment.

‡ A Certificate may be given for such time, OR for such series of experiments as the person signing may think expedient; and it is desirable that such limitation should be here inserted. If a Certificate is unlimited, or limited *by time* only, the Secretary of State usually imposes a limit on the number of experiments to be performed.

‡ This Certificate is given for_____experiments.

‡ This Certificate shall be in force until the_____day of_____19____

This Certificate ceases to have effect on the expiration of the Licence.

Signature of Certifiers to be attached here

Date _____

§ *At the end of the Description the animals are to be named, and it is necessary to submit, in addition, if dogs or cats are used, Certificate E, or if horses, asses or mules are used, Certificate F.*

§ Description of proposed experiments.

N.B.—This Certificate is subject to any conditions that may be assigned in the Licence, and it will be the duty of the holder to refer to his Licence and ascertain whether any of the conditions attached to the Licence limit the number of experiments authorized by this Certificate, or in any other way place restrictions on what may be done under this Certificate.

CERTIFICATE B.

WHEREAS *

has represented to us †

that he proposes, if duly authorized under the above-mentioned Act, to perform on living animals certain experiments described below, such animals being, during the whole of the initial operation of such experiments, under the influence of some anæsthetic of sufficient power to prevent their feeling pain. We hereby certify that, in our opinion, the killing of the animal on which any such experiment is performed before it recovers from the influence of the anæsthetic administered to it would necessarily frustrate the object of such experiment.

* Here insert name, address, and profession of person to whom Certificate is to be given. (Sec. 11 of Act.)

† Here insert name, address, and statutory qualification of each person certifying. (Sec. 11 of Act.)

‡ This Certificate is given for_____experiments.

‡ This Certificate shall be in force until the_____day of_____19____

‡ A Certificate may be given for such time, OR for such series of experiments as the person signing may think expedient; and it is desirable that such limitation should be here inserted. If a Certificate is unlimited, or limited *by time* only, the Secretary of State usually imposes a limit on the number of experiments to be performed.

This Certificate ceases to have effect on the expiration of the Licence.

Signature of Certifiers to be attached here }

Date _____

§ Description of proposed experiments.

§ *At the end of the Description the animals are to be named, and it is necessary to submit, in addition, if dogs or cats are used, Certificate EE, or if horses, asses or mules are used, Certificate F.*

N.B.—This Certificate is subject to the conditions laid down by the Act and to any conditions that may be assigned in the Licence, and it will be the duty of the holder to refer to his Licence and ascertain whether any of the conditions attached to the Licence limit the number of experiments authorized by this Certificate, or in any other way place restrictions on what may be done under this Certificate.

CERTIFICATE C.

WHEREAS *

* Here insert name, address, and profession of person to whom Certificate is to be given. (Sec. 11 of Act.)

has represented to us †

† Here insert name, address, and statutory qualification of each person certifying. (Sec. 11 of Act.)

that he proposes, if duly authorized under the above-mentioned Act, to perform at

by way of illustration of lectures to be there delivered, certain experiments described below on living animals, such experiments being performed under the provisions contained in the said Act as to the use of anæsthetics: We hereby certify that, in our opinion, the proposed experiments are absolutely necessary for the due instruction of persons to whom such lectures are to be given, with a view to their acquiring physiological knowledge, or knowledge which will be useful to them for saving or prolonging life or alleviating suffering.

This Certificate ceases to have effect on the expiration of the Licence.

‡ The animal must during the whole of the experiment be under the influence of some anæsthetic of sufficient power to prevent the animal feeling pain; and the animal must, if the pain is likely to continue after the effect of the anæsthetic has ceased, or if any serious injury has been inflicted on the animal, be killed before it recovers from the influence of the anæsthetic which has been administered. Sec. 8 (3) and (4).

Signatures of Certifiers to be attached here } †

Date

‡ Description of proposed experiments.

N.B.—This Certificate is subject to any conditions that may be assigned in the Licence, and it will be the duty of the holder to refer to his Licence and ascertain whether any of the conditions attached to the Licence limit the number of experiments authorized by this Certificate, or in any other way place restrictions on what may be done under this Certificate.

CERTIFICATE D.

WHEREAS †

has represented to us ‡

that he proposes, if duly authorized under the above-mentioned Act, to perform on living animals certain experiments described below, for the purpose of testing the former discoveries described below, alleged to have been made for the advancement of physiological knowledge, or knowledge which will be useful for saving or prolonging life or alleviating suffering: We hereby certify that, in our opinion, such testing is absolutely necessary for the effectual advancement of such knowledge.

† Here insert name, address, and profession of person to whom Certificate is to be given. (Sec. 11 of Act.)

‡ Here insert name, address, and statutory qualification of each person certifying. (Sec. 11 of Act.)

§ This Certificate is given for_____experiments.

§ This Certificate shall be in force until the_____day of_____19____.

§ A Certificate may be given for such time or for such series of experiments as the person signing may think expedient, and it is desirable that such limitation should be here inserted. If a Certificate is unlimited, or limited by *time only*, the Secretary of State usually imposes a limit on the number of experiments to be performed.

Signatures of Certifiers to be attached here } ‡

Date

* Description of proposed experiments.	Description of former discoveries for the purpose of testing which the proposed experiments are to be made.

* This Certificate, when required, is in addition to any other Certificates that may be required for the same experiments. The experiments should be described alike in all the Certificates.

N.B.—This Certificate is subject to any conditions that may be assigned in the Licence, and it will be the duty of the holder to refer to his Licence and ascertain whether any of the conditions attached to the Licence limit the number of experiments authorized by this Certificate, or in any other way place restrictions on what may be done under this Certificate.

CERTIFICATE E.

WHEREAS *

has represented to us †

that he proposes, if duly authorized under the above-mentioned Act, to perform on dogs and cats the experiments described below without anæsthetics: We hereby certify that, in our opinion, for the reasons specified below, the object of any such experiment will be necessarily frustrated unless it is performed on an animal similar in constitution and habits to a dog or cat, and that no other animal is available for any such experiment.

‡ This Certificate is given for _____ experiments.

‡ This Certificate shall be in force until the _____ day of _____ 19____

Signatures of Certifiers to be attached here †

Date _____

§ Description of experiments to be performed.

Reasons why the object of any such experiment will be necessarily frustrated unless it is performed on an animal similar in constitution and habits to a dog or cat, and why no other animal is available for any such experiment.

N.B.—This Certificate is subject to any conditions that may be assigned in the Licence, and it will be the duty of the holder to refer to his Licence and ascertain whether any of the conditions attached to the Licence limit the number of experiments authorized by this Certificate, or in any other way place restrictions on what may be done under this Certificate.

* Here insert name, address, and profession of person to whom Certificate is to be given. (Sec. 11 of Act.)

† Here insert name, address, and statutory qualification of each person certifying. (Sec. 11 of Act.)

‡ A Certificate may be given for such time or for such series of experiments as the person signing may think expedient, and it is desirable that such limitation should be here inserted. If a Certificate is unlimited, or limited *by time only*, the Secretary of State usually imposes a limit on the number of experiments to be performed.

§ *This Certificate never stands alone, but if it is necessary it accompanies Certificate A, and the description of the experiments in this Certificate should be identical with the description in Certificate A. This Certificate is not required when experiments are performed under the Licence alone.*

CERTIFICATE EE.

WHEREAS *

has represented to us †

that he proposes, if duly authorized under the above-mentioned Act, to perform on living animals certain experiments described below, such animals being, during the whole of the initial operation of such experiments under the influence of some anæsthetic of sufficient power to prevent their feeling pain; and that he is submitting to the Secretary of State a Certificate B, which, if not disallowed, will dispense from the statutory obligation to kill the animal on which any such experiment is performed before it recovers from the influence of the anæsthetic. We hereby certify that, in our opinion, for the reasons specified below, the object of any such experiment will be necessarily frustrated unless it is performed on an animal similar in constitution and habits to a dog or cat, and that no other animal is available for any such experiment.

‡ This Certificate is given for_____experiments.

‡ This Certificate shall be in force until the_____day of_____19____.

This Certificate does not come into operation until one week after a copy has been forwarded to the Secretary of State, and even if given for a longer period ceases to have effect on the expiration of the Licence.

Signatures of Certifiers to be attached here

Date _____

§ Description of experiments to be performed :—

Reasons why the object of any such experiment will be necessarily frustrated unless it is performed on an animal similar in constitution and habits to a dog or cat, and why no other animal is available for any such experiment :—

N.B.—This Certificate is subject to the conditions laid down by the Act and to any conditions that may be assigned in the Licence, and it will be the duty of the holder to refer to his Licence and ascertain whether any of the conditions attached to the Licence limit the number of experiments authorized by this Certificate, or in any other way place restrictions on what may be done under this Certificate.

* Here insert name, address, and profession of person to whom Certificate is to be given. (Sec. 11 of Act.)

† Here insert name, address, and statutory qualification of each person certifying. (Sec. 11 of Act.)

‡ A Certificate may be given for such time or for such series of experiments as the person signing may think expedient, and it is desirable that such limitation should be here inserted. If a Certificate is unlimited, or limited *by time* only, the Secretary of State usually imposes a limit on the number of experiments to be performed.

§ *This Certificate never stands alone, but if it is necessary it accompanies Certificate B, and the description of the experiments in this Certificate should be identical with the description in Certificate B. This Certificate is not required when experiments are performed under the Licence alone.*

CERTIFICATE F.

WHEREAS *

has represented to us †

that he proposes, if duly authorized under the above-mentioned Act, to perform on horses, asses, or mules, the experiments described below: We hereby certify that, in our opinion, for the reasons specified below, the object of any such experiment will be necessarily frustrated unless it is performed on a horse, ass, or mule, and that no other animal is available for such experiment.

‡ This Certificate is given for_____experiments.

‡ This Certificate shall be in force until the_____day of_____19____

Signatures of Certifiers † to be attached here

Date _____

§ Description of experiments to be performed.

Reasons why the object of any such experiment will be necessarily frustrated unless it is performed on a horse, ass, or mule, and why no other animal is available for any such experiment.

N.B.—This Certificate is subject to any conditions that may be assigned in the Licence, and it will be the duty of the holder to refer to his Licence and ascertain whether any of the conditions attached to the Licence limit the number of Experiments authorized by this Certificate, or in any other way place restrictions on what may be done under this Certificate.

* Here insert name, address, and profession of person to whom Certificate is to be given. (Sec. 11 of Act.)

† Here insert name, address, and statutory qualification of each person certifying. (Sec. 11 of Act.)

‡ A Certificate may be given for such time or for such series of experiments as the person signing may think expedient, and it is desirable that such limitation should be here inserted. If a Certificate is unlimited, or limited *by time* only, the Secretary of State usually imposes a limit on the number of experiments to be performed.

§ *This Certificate is always required when experiments are performed on horses, asses, or mules, and, in addition, there will be required, if the experiments are to be performed without anæsthetics, Certificate A, or if the experiments are under anæsthetics, but the animals are to remain alive after anæsthesia has ceased, Certificate B. It is necessary that the description of the experiments should be the same in all the Certificates.*

II.—Anæsthetics Used for Animals.

In almost every case, the anæsthetic used is chloroform or ether, sometimes combined with or followed by morphia or chloral. The nature of the anæsthetic used in each case must, of course, be stated in the returns sent to the Home Office. Of the use of ether, it need only be said that animals take it well, and that there is no difficulty in rendering them unconscious with it.

With some animals chloroform is equally good; with others it is dangerous to life. But Professor Hobday, of the Royal Veterinary College, has published an account of five hundred administrations of chloroform to dogs, for the operations of veterinary surgery, with only one death. (*Lancet*, September 1898.) Still, for dogs and cats, ether is used in preference to chloroform. Other animals take chloroform well.* And it is wholly false to say that "just a whiff" of chloroform or ether is

* The *Veterinary Record* (1899) published an excellent paper by Mr Tasker on the best method of administering chloroform to horses; and the *Lancet*, 18th February 1899, says, in a review of it, "We fear that much unnecessary suffering to animals has in the past been allowed through the dread of incurring the supposed risk of giving chloroform to valuable horses, dogs, etc. As has been pointed out by Mr Hobday and others, the lower animals can be most successfully given chloroform if they are properly dealt with, if a rational method is adopted, and if the management of the anæsthetic is committed to a trained person, and not entrusted to a stable helper or a rustic, who is as incapable of giving chloroform to a horse as to a human being."

given, or "just enough to keep the animal quiet." Lately, in an account of some experiments, it was stated that in two or three cases the anæsthesia was incomplete. Such use of chloroform or ether may be made, for good reasons, in certain surgical procedures, or for the alleviation of the pains of childbirth: but alike in surgery and in experiments on animals it is altogether exceptional, or something more than exceptional.

Morphia is seldom used alone; but in some cases it is used after chloroform or ether. It is certain that an animal, so far under the influence of morphia that it lies still, cannot be suffering; for the drug does not act directly on the muscles, but on the higher nervous centres. And, for the purposes of the experiment—to put the matter on the lowest ground—the animal must be kept at rest.

It has been said that "morphia acts upon dogs as a violent stimulant rather than as a narcotic, large doses causing excitement and convulsions." The reference is to an account, in the *British Medical Journal*, 14th January 1899, of a paper by Professor Lugaro, of Florence, on certain microscopic varicosities on the terminal filaments (dendrites) of the nerve-cells of the surface of the brain. These infinitely minute varicosities are said to contract when the brain is active or fatigued, and expand when it is at rest; and Lugaro's study of this vanishing-point of structure is the last word, at present, on the physical changes in sleep and unconsciousness. He used various

anæsthetics and narcotics in his experiments, not so much to allay pain, for the experiments can hardly be called painful—the animals were killed by an instantaneous method of injection—but that the nerve-cells of the brain might be caught and fixed at the moment of contraction or expansion of the varicosities of their terminal filaments. The purpose of the chloroform, ether, morphia, and chloral, that he used, was to produce diverse conditions, such as obtain during cerebral action or inaction. There was no operation save that necessary for the injection into a vessel, and then instantaneous death. In animals that had been excited by morphia, as some men and women are excited by it, the brain-cells under the microscope still registered the mental state at the moment of death. It happens, now and again, that a dog is not influenced by morphia, is excited, not narcotised, by it. But this is altogether exceptional; an animal in such a condition could not be used for experiment; and the physiologist has other anæsthetics. Except in these rare cases, animals take morphia well, and are profoundly influenced by it.

Curare is not an anæsthetic under the Act. In 1875-76, the evidence as to its action was somewhat unsettled; but most of the witnesses held that it acted only on the motor system, and had no anæsthetic influence. It was therefore ruled out by the Act; and its use was thus defined in 1899, by the Home Secretary:—

"It is illegal to use curare as an anæsthetic. It is often used in addition to anæsthetics, for very

good reasons; and, as it does not render an anæsthetised animal sensitive, it would be absurd to forbid its use."

Some of those who are opposed to all experiments on animals say that the operation is done under chloroform or ether—what they call "a whiff of chloroform"—and the animal is then subjected to horrible tortures heightened by curare. But, apart from the fact that the internal organs, even in man, are so little sensitive to touch that they may be called insensitive, and apart from the fact that morphia is combined with curare, there is evidence that curare, in such doses as are given in those few cases where it is used, acts not only on the motor system but also on the sensory system :—

"It is quite true that curare in small doses has the effect of paralysing the motor nerves without affecting the nerves of sense; but in such doses as are used in the laboratory, it paralyses both sets of nerves, and this has actually been proved on man, as there have been cases of accidental curare poisoning in men who recovered, and in whom sensation has been totally abolished, while the action of the drug was apparent. Moreover, curare is nowadays not used alone, but is always used in combination with morphia, ether, chloroform, or other anæsthetics." (Professor Rüffer, *Liberty Review*, October 1893.)

"Much indignation has been felt about the use of curare, and the Act of 1876 expressly forbids its use as an anæsthetic. When it is used, it must be supplemented with some other drug to relieve pain. A good deal of misconception exists as to the

actual physiological effect of curare, or woorali, or oorali, as it is variously called. It is the arrow poison of Guiana. It undoubtedly shows its effects first upon the muscles and their nerves. It kills by arresting respiration, by paralysing the respiratory muscles. It is a powerful poison, and unless respiration is maintained artificially the animal dies asphyxiated. Claude Bernard believed that it did not in any way affect the sensory nerves, and he described in theatrical terms the animal as being unable to stir, but suffering horrible torture. . . . It is pretty certainly known now that Claude Bernard was wrong, and that, though curare acts first upon the motor nerves, it also, though less rapidly, paralyses the sensory nerves, always supposing that by artificial respiration the animal is kept alive long enough for the less rapid effect to be produced. It would be out of place here to give the experimental evidence which satisfies physiologists upon this point. One case only is known to have occurred in which the full influence of curare could be studied upon a human being, and in which at the same time the presence or absence of anæsthetic effect could be noted. The case is reported by Mr Joseph White, late of Nottingham, and a former President of the British Medical Association. A servant-girl accidentally transfixed her arm with a poisoned arrow while dusting a trophy of Indian arms in her master's hall. The arrow was withdrawn within two minutes, and the girl was seen by Mr White half an hour later. She was then collapsed, and was breathing very badly. Artificial respiration was kept up, aided by faradisation. The wound was freely excised along its entire length. Two hours later reaction set in, and the patient gradually recovered. On regaining consciousness, she ex-

pressed the utmost surprise at seeing the wound in her arm, as she had felt nothing of the operation. She had, in fact, been unconscious from within half an hour of the poison. Had Claude Bernard's dictum been correct, she ought, though paralysed as to her muscles, to have been throughout the whole time conscious and sensitive. Probably the truth is that, like all other nerve-poisons, the effect of curare varies with the dose. The muscular nerves are the first affected, then the sensory, and finally the central nervous system. As a matter of fact, however, morphia or some other narcotic is always given in addition to curare when it is used in laboratory work in England." (*Edinburgh Review*, July 1899.)

Here are two very definite statements of the action of curare: one by Professor Rüffer, who was in 1893 Hon. Secretary of the Institute of Preventive Medicine; the other by a writer who seems to speak from experience. Anyhow, curare is not an anæsthetic under the Act: and, in the United Kingdom, it is seldom used at all, and never alone, in any experiment involving any sort or kind of painful operation. In every case of this kind, a recognised anæsthetic must be given, and is given.

III.—Reports of Inspectors under the Act.

The Annual Reports of the Inspectors under the Act can be procured from Messrs Eyre & Spottiswoode, Government Publishers, East Harding Street, London, E.C. For want of space, only the three last reports can be put here, without their tables.

1899.

ENGLAND AND SCOTLAND.

Sir, May 10, 1900.

I have the honour to submit the following Report on Experiments performed in England and Scotland during the year 1899, under the Act 39 and 40 Vict. c. 77, including,—

I. The Names of all Persons who have held Licenses or Special Certificates during any part of the Year; together with a Statement of the Registered Places at which the Licenses were valid, and of the Persons who signed the Applications for Licenses and granted Certificates under the Act.

II. The total Number of Experiments performed during 1899, classified and arranged according to their general Nature.

Report.

The names of all those persons who held licenses during 1899 will be found in Tables I. and II. The total number of licensees was 250, of whom 72 performed no experiments.

The names of all those "registered places" to which licensees were accredited are given in the tables. All licensees were restricted to the registered place or places specified on their licenses, with the exception of those who were permitted to perform inoculation experiments in places other than a "registered place," with the object of studying outbreaks of disease among animals in remote districts.

Tables I. and II. afford evidence,—

1. That licenses and certificates have been granted and allowed only upon the recommendation of persons of high scientific standing;

2. That the licensees are persons who, by their training and education, are fitted to undertake experimental work and to profit by it;

3. That all experimental work has been conducted in suitable places.

Table III. shows the number and the nature of the experiments performed by each licensee mentioned in Table I., specifying whether these experiments were done under the license alone or under any special certificate, so that the reader may judge which experiments (if any) were of a painful nature.

Table III. is divided into two parts, A. and B., for the purpose of separating experiments which are performed without anæsthetics from experiments in which anæsthetics are used. The only experiments performed without anæsthetics are inoculations, hypodermic injections, vaccinations, and similar proceedings, in which the pain inflicted is not greater than the prick of a needle. No experiments requiring anything of the nature of a surgical operation, or that would cause the infliction of an appreciable amount of pain, are allowed to be performed without an anæsthetic.

The total number of experiments included in Table III. (A.) is 1656.

Of these there were performed,—

Under License alone . . .	820
„ Certificate C . . .	182
„ Certificate B . . .	449
„ Certificate B + EE . . .	205

In experiments performed under the license alone, or under Certificate C, the animal suffers no pain, because it is kept under the influence of an anæsthetic from the beginning of the experiment until it is killed.

In experiments performed under Certificate B (or EE or F linked with B) the animal is anæsthetised during the operation, but is allowed to recover. These operations, in order to ensure success, are necessarily done with as much care as are similar operations upon the human subject, and the operations being performed aseptically, the process of healing takes place without pain.

Inoculations made (upon rodents) with the object of diagnosing rabies in dogs have been placed, together with

other inoculations requiring a preliminary incision in order to expose the part into which the injection is made, in Table III. (A.). In all these cases the whole operation is performed under an anæsthetic.

The inoculations for the diagnosis of rabies are made in accordance with the directions printed upon the back of dog licenses, which run as follows:—

> "If a dog suspected of being rabid is killed after "it has bitten any person or animal, a veterinary "surgeon should be requested to forward the spinal "cord to the Brown Institution, Wandsworth Road "(or some other licensed institution), in order that it "may be ascertained with certainty whether the "animal was suffering from rabies."

The number of inoculations for the diagnosis of rabies performed in 1899 was 164, the steady decrease during recent years noticed in the report for 1898 having been maintained.

The return of experiments performed by one licensee, holding a license only, has not been received, owing to his absence on service with the forces in South Africa.

Table III. (B.) is devoted entirely to inoculations, hypodermic injections, and some few other proceedings, performed without anæsthetics. It includes 6813 experiments, whereof there were performed,—

Under Certificate A . . .	6689
„ Certificate A + E . . .	83
„ Certificate A + F . . .	41

A large number of these experiments were performed as a matter of professional duty for the diagnosis and prevention of disease, for the standardisation of remedies, and for the testing of articles of food, such as water, milk and butter, many of them on behalf of Government Departments, County Councils, and Municipal Corporations. The demand for antitoxins continues to increase, and during the past year 54,569 doses of diphtheria antitoxin have been sent out from two institutions.

It will be noticed that the number of experiments included in Table III. (A.) shows an increase in comparison with the number in 1898 (1511), while those included in Table III. (B.) have diminished (6813 against 7640). This is in some measure due to the transference of a certain class of inoculations, mainly for the diagnosis of rabies, from Table III. (B.) to Table III. (A.). The total number of experiments (8469) is somewhat less that in 1898 (9151).

During the year the usual inspections of registered places have been made by Dr Poore, Sir James Russell, and myself, and have been severally reported. These inspections have generally been made without notice, the only exceptions in this respect being in cases where it was desired for some reason to meet the licensees at their registered places. I have on several occasions seen animals under experiment, always in a state of profound anæsthesia. The animals being experimented on under Certificates A and B have been carefully examined, and among the large number that I have seen there have been none showing any signs of pain. The guinea-pigs and rabbits for example, which have been inoculated under Certificate A for the testing of antitoxins, for the diagnosis of disease, and so forth, are generally indistinguishable from the untouched animals in stock; and in most cases that have come under my notice of animals operated on under Certificate B, it would be quite impossible, apart from the scar or healing wound, to recognise that anything had been done to them.

I have found the licensees in all cases desirous of acting in strict accordance with the spirit as well as the letter both of the Act and of the special conditions attached to their licenses; and the instances of irregularity which it has been my duty to bring to your notice may be termed accidental, having been due either to misunderstanding or inadvertence. They are as follows :—

A licensee who held Certificates A and E (dispensing with anæsthetics) performed two experiments which were required in the discharge of his duties as Medical Officer of Health, but which were not covered by the terms of his certificates. He reports that the animals suffered no pain; and the failure to

apply for the proper certificates was an oversight, for which an appropriate caution has been administered.

In connection with a pathological research carried on under his direction by a gentleman who held no license, a licensee made himself responsible for a few inoculations under anæsthetics on kittens, although he did not hold the necessary special certificate for those animals. The error was unintentional, and the experiments were duly reported. The licensee was censured for his carelessness.

A licensee in the early part of the year performed two diagnostic inoculations without authority, in the belief that his Certificate A, which expired at the end of 1898, was still in force.

In two cases licensees have allowed persons who did not hold licenses to perform experiments with them, or under their direction, in each instance on three animals. The licensees have been severely censured. It must be clearly understood that licensees cannot delegate their powers to others, or authorise non-licensed persons to perform experiments for them; and steps are being taken to bring this prominently to the notice of licensees and the authorities controlling registered places.

I have the honour to be, Sir,
Your obedient Servant,
G. D. THANE,
Inspector.

The Right Hon. Sir Matthew White Ridley, Bart., M.P.,
Her Majesty's Principal Secretary of State.

1899.

IRELAND.

Sir, 18th May 1900.

I have the honour to submit Tables showing the Experiments performed in Ireland during the year 1899, under the Act 39 and 40 Vict. c. 77.

Nine licenses were in existence during the year. Of these, four expired, one was renewed, and two new licenses were granted.

The certificates in existence or allowed during the year were:—

A, to one licensee.
B, to five licensees.
C, to one licensee.
E, to one licensee.
EE, to one licensee.

Certificate C was disallowed in one instance.

The experiments performed were 227 in number; 79 being under license alone, and 148 under certificates. Two licensees performed no experiments.

The animals experimented on were:—

Rabbits	171
Dogs	43
Guinea-pigs	12
Rat	1

The experiments appear to have been of a useful character, and either painless, or painful only to a slight extent. The bulk of them were inoculations for the diagnosis of diseases, such as canine rabies and tuberculosis.

I have the honour to be,
Sir,
Your obedient Servant,
W. THORNLEY STOKER,
Inspector for Ireland.

To the Right Hon.
The Chief Secretary for Ireland.

1900.

ENGLAND AND SCOTLAND.

Sir, April 27, 1901.

I have the honour to submit the following Report on Experiments performed in England and Scotland during the year 1900, under the Act 39 and 40 Vict. c. 77, including,—

(*a.*) The Names of all Persons who have held Licenses or Special Certificates during any part of the Year; together with a Statement of the Registered Places at which the Licenses were valid, and of the Persons who signed the Applications for Licenses and granted Certificates under the Act.

(*b.*) The total Number of Experiments performed during 1900, classified and arranged according to their general Nature.

Report.

The names of all those persons who held licenses during 1900 will be found in Tables I. and II. The total number of licensees was 247, of whom 63 performed no experiments.

The names of all those "registered places" to which licensees were accredited are given in the tables. All licensees were restricted to the registered place or places specified on their licenses, with the exception of those who were permitted to perform inoculation experiments in places other than a "registered place," with the object of studying outbreaks of disease among animals in remote districts.

Tables I. and II. afford evidence,—

1. That licenses and certificates have been granted and allowed only upon the recommendation of persons of high scientific standing;

2. That the licensees are persons who, by their training and education, are fitted to undertake experimental work and to profit by it;

3. That all experimental work has been conducted in suitable places.

Table III. shows the number and the nature of the experiments performed by each licensee mentioned in Table I., specifying whether these experiments were done under the license alone or under any special certificate.

Table III. is divided into two parts, A. and B., for the purpose of separating experiments which are performed without anæsthetics from experiments in which anæsthetics are used.

The total number of experiments included in Table III. (A.) is 1885.

Of these there were performed,—

Under License alone *	.	1118
„ Certificate C	.	181
„ Certificate B	.	358
„ Certificate B + EE	.	228

Table III. (B.) is devoted entirely to inoculations, hypodermic injections, and some few other proceedings, performed without anæsthetics. It includes 8954 experiments, whereof there were performed,—

Under Certificate A	.	8825
„ Certificate A + E	.	117
„ Certificate A + F	.	12

The total number of experiments is 10,839, being 2370

* In experiments performed under license alone, the animal must during the whole of the experiment be under the influence of some anæsthetic of sufficient power to prevent the animal feeling pain; and the animal must, if the pain is likely to continue after the effect of the anæsthetic has ceased, or if any serious injury has been inflicted on the animal, be killed before it recovers from the influence of the anæsthetic which has been administered.

Certificate C allows experiments to be performed, under the foregoing provisions as to the use of anæsthetics, in illustration of lectures.

Certificate B exempts the person performing the experiment from the obligation to cause the animal on which the experiment is performed to be killed before it recovers from the influence of the anæsthetic; and when the animal is a dog or a cat, Certificate EE is also necessary.

Certificate A allows experiments to be performed without anæsthetics; and when the animal on which the experiment is performed is a dog or a cat, Certificate E is also necessary.

Certificate F is required in all cases of experiments on a horse, ass, or mule.

more than in 1899 ; the increase in the number of experiments included in Table III. (A.) is 229, and in Table III. (B.) 2141.

But few of these experiments have been in any serious degree painful. Taking first the experiments recorded in Table III. (A.), 1885 in number, the experiments performed under license alone, or under Certificate C, together amounting to 1299, are unattended by pain, because the animal is kept under an anæsthetic during the whole of the experiment, and must, if the pain is likely to continue after the effect of the anæsthetic has ceased, or if any serious injury has been inflicted on the animal, be killed before it recovers from the influence of the anæsthetic.

In the remaining 586 experiments, performed under Certificate B, or B linked with EE, the operations are performed under anæsthetics, from the influence of which the animals are allowed to recover. The operations are performed aseptically, and the healing of the wounds as a rule takes place without pain. If the antiseptic precautions fail and suppuration occurs, the animal is required to be killed. These operations as now practised are seldom, if ever, followed by pain. I have seen numerous animals on which serious operations have been performed, removal of organs and the like, and which were clearly not in pain ; indeed, they were often to all appearance in perfect health.

The experiments included in Table III. (B.), 8954 in number, are all performed without anæsthetics. They are mostly inoculations, but a few are feeding experiments, or the administration of various substances by the mouth. In no case has a certificate dispensing with the use of anæsthetics been presented for an experiment involving a serious operation.

The pain caused by a hypodermic injection is so slight that such a procedure in itself could hardly be regarded as coming under the Act. But the experiment does not terminate with the injection. The effect of the injection may be to set up a condition of disease accompanied by pain, and the experiment continues until the animal recovers, or dies, or is killed. This effect may not manifest itself for a considerable time, extending perhaps over several days, and the certificate dispensing

with the use of anæsthetics is necessary, in addition to the license, since it is evident that the experiment could not be performed if the animal had to be kept under an anæsthetic during the whole period from the administration of the injection until the close of the experiment.

It must not be assumed that the animal is in pain during the whole of this time. In cases of prolonged action of an injected substance, even when ending fatally, the animal is generally apparently well, and takes its food as usual, until a short time before death. The state of illness may last only a very few hours, and in some cases it is not observed at all.

In a large proportion of the inoculations included in Table III. (B.), the result is negative; that is, the animal does not exhibit any ill effects, and therefore does not suffer any pain. This is especially the case with many inoculations for purposes of diagnosis, with the great majority of the inoculations performed for the testing of articles of food, and with many of the inoculations made for the purpose of standardising antitoxic serum, namely, those cases in which the antitoxin is sufficiently powerful to neutralise the amount of toxin injected, so that the latter has no action. It is only a small proportion of the inoculations practised that are followed by disease or poisoning. In some of these cases, such as the injection of certain drugs, or of tetanus toxin, the effect produced is without doubt painful; but in the two most frequently employed proceedings of this kind, viz., inoculation for the diagnosis of tuberculosis, and for the standardisation of diphtheria antitoxin, there is some difference of opinion amongst those who have had most experience as to whether the effects produced are attended by pain or not. There is, however, strong reason for holding that the gradual development of tuberculosis and the poisoning by diphtheria toxin resulting from such inoculations, although they may not be accompanied by acute suffering, are conditions which bring these proceedings within the category of "experiments calculated to give pain."

In the event of pain ensuing as the result of an inoculation, a condition attached to the license requires that the animal shall be killed under anæsthetics as soon as the main result of the experiment has been attained.

It will be seen, therefore, that in a very large number of instances, especially in the case of experiments performed without the use of anæsthetics, the experiments are entirely painless. Such experiments are performed under license and certificates, because it is impossible to foretell in an individual case whether painful consequences will ensue. Considerable difficulty is also frequently experienced in deciding whether a contemplated procedure is calculated to give pain or not, and in such doubtful cases the experimenter applies for a license, and procures the certificates necessary to cover his proceedings.

During the past year the attention of the Secretary of State was called to certain experiments in which animals were deprived of food for variable periods. The licensee explained that he did not deem these experiments to be within the scope of the Act 39 and 40 Vict. c. 77. Inasmuch as a full account of these experiments was published in 1896, and they were not brought to the notice of the Secretary of State at the time, it was decided that it was too late to institute proceedings with a view to determining whether these experiments came under the Act or not. At the same time, the Secretary of State expressed his opinion that experiments involving starvation to an extent calculated to cause pain were undoubtedly within the Act.

The large increase in the number of inoculation experiments included in Table III. (B.) is mainly due to the growing appreciation of their great value as a means of detecting, curing, and preventing disease. Inoculations for the purpose of diagnosis are now part of the routine of medical practice; during the year 1900, 2230 inoculations were made by three licensees for the purpose of standardising antitoxins, and over 1500 inoculations were made by two licensees for the testing of milk. These experiments are performed in large numbers on behalf of the authorities responsible for the care of the Public Health, including the Local Government Board, County Councils, and Municipal Corporations.

The appearance of bubonic plague in this country has afforded an illustration of the value of the experimental method in diagnosis. It is of the greatest importance that this disease should be recognised as early as possible. This can only be

done with certainty with the aid of inoculations into animals. Two fresh places were registered, and two new licenses were granted during 1900, expressly to allow of the necessary experiments being performed in localities where infection was apprehended.

The number of inoculations for the diagnosis of rabies in dogs has fallen to 81 for the year 1900.

Returns of experiments have not been received from two licensees, who are on service in South Africa. They are believed not to have performed any experiments, and their names are placed provisionally in Table II.

The licensee, whose return for 1899 had not been received at the time when last year's report was submitted, has since reported six experiments under license alone.

During the year the usual inspections of registered places have been made by Sir James Russell and myself, and have been severally reported. We have found the animals everywhere suitably lodged and well cared for. In a place where the accommodation for animals was considered defective, registration was withheld.

I have had to report the following irregularities :—

1. A licensee holding the certificate dispensing with the use of anæsthetics, performed some inoculations under anæsthetics, allowing the animals to recover therefrom. The animals suffered no pain. This is an irregularity, because the certificate (B) required by the Act when an anæsthetic is used, and the animal allowed to recover therefrom, is different from the certificate (A) required when an experiment is performed entirely without anæsthetics.

2. In another case, a licensee holding the certificate (B), exempting from the obligation to kill the animal before it recovers from the influence of the anæsthetic, reported as being performed under this certificate, seven experiments in which drugs were administered by the mouth and by injection without anæsthetics. It is doubtful whether the administration of these drugs actually caused pain ; but, if so, and the experiments therefore came under the Act, the licensee should have obtained the certificate (A) dispensing with the use of anæsthetics.

3. A licensee, through a misunderstanding, performed a larger number of inoculations without anæsthetics than was authorised by his certificate. The mistake was clearly unintentional, and the licensee has been cautioned.

4. A licensee, not holding the special certificate necessary for the purpose, made two inoculations upon guinea-pigs under the influence of an anæsthetic, and allowed the animals to recover therefrom. The object of the experiments was the detection of tuberculosis, and the result being negative the animals suffered no pain. Before these experiments, which might have caused pain to the animals, were undertaken, a certificate ought to have been obtained by the licensee, who has been accordingly cautioned as to his future proceedings should he desire a renewal of his license.

5. A licensee, holding no certificates, performed operations on rabbits under an anæsthetic, and allowed them to recover. The operation was not severe, and the animals have remained in good health. For these experiments the licensee required a certificate (B). He has been censured, and has not sought a renewal of his license.

I have the honour to be, Sir,
Your obedient Servant,
G. D. THANE,
Inspector.

The Right Hon. Charles Thomson Ritchie, M.P.,
His Majesty's Principal Secretary of State.

1900.

IRELAND.

REPORT.

Sir, 13th February 1901.

I have the honour to submit Tables showing the Experiments performed in Ireland during the year 1900, under the Act 39 and 40 Vict. c. 77.

Six licenses were in existence during the year. Of these, one expired, but was renewed.

The certificates in existence or allowed during the year were :—

A, to one licensee.
B, to four licensees.
E, to one licensee.

The experiments performed were 135; 3 being under license alone, and 132 under certificates. One licensee performed no experiments, and another being at present on a sea voyage, has made no return.

The animals experimented on were :—

Rabbits	109
Guinea-pigs	17
Mice	8
Cat	1

The experiments performed have been of a useful character, and attended by little or no pain. They were chiefly done in connection with the identification of canine rabies and tuberculosis, or the investigation of tetanus and epidemic cerebro-spinal meningitis.

I have the honour to be,
Sir,
Your obedient Servant,
W. THORNLEY STOKER,
Inspector for Ireland.

To the Right Hon.
The Chief Secretary for Ireland.

1901.

ENGLAND AND SCOTLAND.

Sir, April 2nd, 1902.

I have the honour to submit the following Report on Experiments performed in England and Scotland during the year 1901, under the Act 39 and 40 Vict. c. 77, including,—

(*a.*) The Names of all Persons who have held Licenses or Special Certificates during any part of the Year; together with a Statement of the Registered Places at which the Licenses were valid, and of the Persons who signed the Applications for Licenses and granted Certificates under the Act.

(*b.*) The total Number of Experiments performed during 1901, classified and arranged according to their general Nature.

Report.

The names of all those persons who held licenses during 1901 will be found in Tables I. and II. The total number of licensees was 257, of whom 56 performed no experiments.

The names of all those "registered places" to which licensees were accredited are given in the tables. All licensees were restricted to the registered place or places specified on their licenses, with the exception of those who were permitted to perform inoculation experiments in places other than a "registered place," with the object of studying outbreaks of disease among animals in remote districts.

Tables I. and II. afford evidence,—

1. That licenses and certificates have been granted and allowed only upon the recommendation of persons of high scientific standing;

2. That the licensees are persons who, by their training and education, are fitted to undertake experimental work and to profit by it;

3. That all experimental work has been conducted in suitable places.

Table III. shows the number and the nature of the experiments performed by each licensee mentioned in Table I., specifying whether these experiments were done under the license alone or under any special certificate.

Table III. is divided into two parts, A. and B., for the purpose of separating experiments which are performed without anæsthetics from experiments in which anæsthetics are used.

The total number of experiments included in Table III. (A.) is 2049.

Of these there were performed,—

Under License alone	.	1176
„ Certificate C	.	174
„ Certificate B	.	454
„ Certificate B + EE	.	245

Table III. (B.) is devoted entirely to inoculations, hypodermic injections, and some few other proceedings, performed without anæsthetics. It includes 9596 experiments, whereof there were performed,—

Under Certificate A	.	9504
„ Certificate A + E	.	78
„ Certificate A + F	.	14

The total number of experiments is 11,645, being 806 more than in 1900; the increase in the number of experiments included in Table III. (A.) is 164, and in Table III. (B.) 642.

All experiments involving a serious operation are placed in Table III. (A.). The larger part of the experiments included in this table, viz., all performed under license alone, and under Certificate C, 1350 in number, are unattended by pain, because the animal is kept under an anæsthetic during the whole of the experiment, and must, if the pain is likely to continue after the effect of the anæsthetic has ceased, or if any serious injury has been inflicted on the animal, be killed before it recovers from the influence of the anæsthetic.

In the experiments performed under Certificate B, or B linked with EE, 699 in number, the initial operations are performed under anæsthetics, from the influence of which the animals are allowed to recover. The operations are performed

aseptically, and the healing of the wounds, as a rule, takes place without pain. If the antiseptic precautions fail, and suppuration occurs, the animal is required to be killed. It is generally essential for the success of these experiments that the wounds should heal cleanly and the surrounding parts remain in a healthy condition. Experiments involving the removal of important organs, and even of parts of the brain, are performed without causing pain to the animals; and after the section of a part of the nervous system, the resulting degenerative changes are painless.

In the event of a subsequent operation being necessary in an experiment performed under Certificate B, or B linked with EE, a condition is attached to the license requiring all operative procedures to be carried out under anæsthetics of sufficient power to prevent the animal feeling pain.

In no case has a cutting operation more severe than a superficial venesection been allowed to be performed without anæsthetics.

The experiments included in Table III. (B.), 9596 in number, are all performed without anæsthetics. They are mostly inoculations, but a few are feeding experiments, or the administration of various substances by the mouth, or the abstraction of a minute quantity of blood for examination. In no instance has a certificate dispensing with the use of anæsthetics been allowed for an experiment involving a serious operation. Inoculations into deep parts, involving a preliminary incision in order to expose the part into which the inoculation is to be made, are required to be performed under anæsthetics, and are therefore placed in Table III. (A.).

In the last Report which I had the honour to submit, I explained fully the reasons why inoculation experiments are regarded as being experiments calculated to give pain, and therefore come under the Act 39 and 40 Vict. c. 77. The local affection and the state of illness which may be induced by the inoculation, and which may lead to the death of the animal, although they may not be attended by acute suffering, are of such a nature as to bring these proceedings within the category of "experiments calculated to give pain."

In a very large number of the experiments included in

Table III. (B.), the results are negative, and the animals suffer no inconvenience whatever from the inoculation. These experiments are therefore entirely painless.

In the event of pain ensuing as the result of an inoculation, a condition attached to the license requires that the animal shall be killed under anæsthetics as soon as the main result of the experiment has been attained.

Of the experiments included in Table III. (B.), a large proportion are performed for the diagnosis or treatment of disease, or are necessitated by the requirements of the authorities responsible for the care of the Public Health. Inoculations are frequently essential for diagnosis, especially of tuberculosis, anthrax, glanders, rabies, and bubonic plague. During the year 1901, five licensees performed 2636 inoculation experiments for testing antitoxins; and ten other licensees return 2085 similar experiments, almost all of which were performed in the course of investigations directed by the Local Government Board, County Councils, and Municipal Corporations, more than half being for the testing of milk.

The number of injections made during the year 1901 for the diagnosis of rabies in dogs is 83.

During the year the usual inspections of registered places have been made by Sir James Russell and myself, and have been severally reported. We have found the animals everywhere suitably lodged and well cared for, and the licensees desirous of acting in every way in accordance with the letter and the spirit of the Act. The instances of irregularity are only three in number; two of these are very slight, and were clearly the result of misapprehension; while the third was due to inadvertence. They are as follows:—

In one case a licensee holding the certificate dispensing with the use of anæsthetics, fearing that some pain might be caused to the animal, administered an anæsthetic before making an injection. It has been pointed out to the licensee that the Act requires a different certificate (B) when an anæsthetic is used, and the animal is allowed to recover therefrom, from that (A) authorising experiments to be performed entirely without anæsthetics.

A licensee, holding the special certificates (B + EE) for

performing certain experiments on dogs, performed similar experiments on rabbits, although these animals were not specified on his certificate (B). He had not observed the notice on the certificate (B) that the animals on which experiments will be performed are to be named, and was under the impression that he might perform under this certificate experiments on any animals other than those for which additional special certificates are prescribed. The licensee has been cautioned.

A licensee performed certain experiments for which a certificate (B) was necessary. It appeared that he possessed the certificate, which was duly signed, but had not been submitted to the Secretary of State. The Act requires that a copy of every certificate shall be forwarded by the applicant to the Secretary of State; and the certificate is not available until one week after a copy has been so forwarded. In this case the license was revoked.

I have the honour to be,
Sir,
Your obedient Servant,
G. D. THANE,
Inspector.

The Right Hon. Charles Thomson Ritchie, M.P.,
His Majesty's Principal Secretary of State.

1901.

IRELAND.

REPORT.

Sir, March 20th, 1902.

I have the honour to submit Tables showing the Experiments performed in Ireland during the year 1901, under the Act 39 and 40 Vict. c. 77.

Two new places were registered under the Act during the year; one in the Queen's College, Cork; the other in Limerick. The latter was registered in connection with observations

undertaken by the desire of the Department of Agriculture for Ireland with a view to the study of white scour and lung disease in cattle.

Ten licenses were in existence during the year. Of these, two expired, and their renewal was not sought; three expired and were renewed; three were new licenses.

The certificates in existence or allowed were :—

A, to two licensees.
B, to eight licensees.
E, to one licensee.

The experiments performed were 237; 47 being under license alone and 190 under certificates. Three licensees performed no experiments, and one is absent from Ireland and has made no return. Eleven certificates were in force among eight licensees; only four were acted on, viz., two under Certificate A, and two under Certificate B.

The animals experimented on were :—

Guinea-pigs	116
Rabbits	99
Mice	9
Calves	9
Cows	3
Goat	1

The experiments performed have been of a useful character, and attended by little or no pain. They were all inoculations, and with the exception of ten were all done for the purpose of the diagnosis or investigation of existing diseases. The diseases investigated were canine rabies, tuberculosis, tetanus, typhoid fever, and scour and lung disease in cattle.

I have the honour to be,
Sir,
Your obedient Servant,
W. THORNLEY STOKER,
Inspector for Ireland.

To the Right Hon.
The Chief Secretary for Ireland.

SUMMARY OF REPORTS, ETC.

THESE Reports give a plain answer to some false statements made by the opponents of all experiments on animals. They show that four-fifths of these experiments are "inoculations, feeding-experiments, the administration of various substances by the mouth, or the abstraction of a minute quantity of blood for examination." That is to say, four animals out of every five undergo no sort or kind of operation beyond a hypodermic injection or the lancing of a vein just under the skin. It is in these cases, *and in these cases only*, that no anæsthetic is given. The Report for 1901 (England and Scotland) is quite clear on this point—*In no case has a cutting operation more severe than a superficial venesection been allowed to be performed without anæsthetics.*

They show, also, that the results of inoculation are, *in a very large number of cases, entirely painless.* They do not deny that, in other cases, there is the pain of disease. This pain cannot be more than the pain of the same disease, come in the course of Nature, in the same number of animals bred for profit or kept for pleasure. A pet rabbit, or guinea-pig, that dies of tuberculosis,

has neither more nor less pain than a similar animal inoculated with the disease. The administration of drugs, in a few cases, is painful: the cases are very few, and involve no more pain than is involved in the death by poisoning of the same number of rats and mice in houses.

They show, also, that the majority of these inoculations, etc., are made not as "researches," but in the direct practical service of the public health, or in the interests of agriculture: not to elucidate problems of pathology, but to standardise drugs, to ensure the purity of food, to protect flocks and herds, and so forth. *During the year* 1901, *five licensees performed* 2636 *inoculation experiments for testing antitoxins; and ten other licensees return* 2085 *similar experiments, almost all of which were performed in the course of investigations directed by the Local Government Board, County Councils, and Municipal Corporations, more than half being for the testing of milk.* Beside this national and Governmental work, there are all the inoculations made for the sure and early diagnosis of diseases, whether in hospitals, or in private practices, or in ships under quarantine, or among sheep and cattle.

They show, also, that the question of pain does not arise over the great majority of those experiments which are not inoculations, but operations of more or less severity: for, in this majority, the animal is anæsthetised the whole time, and is killed under the anæsthetic, before it recovers consciousness. These are the experiments made under

a License alone, or under a License and Certificate C. These deaths involve no pain: they may therefore be compared to the same number of deaths inflicted by skilful butchers or skilful sportsmen. In 1901, they numbered between 1300 and 1400. That is to say, they were not more, in a year, than the deaths inflicted in a day, for sport, by ten or twelve big shooting-parties.

The only experiments, other than inoculations, etc., over which the question of pain can possibly be raised, are those made under a License and Certificate B, with or without Certificate EE or Certificate F. These are operations, done under anæsthesia, from which the animal is allowed to recover: for instance, the removal of an organ or part of an organ, the section of a nerve, the establishment of a fistula, the ligature of an artery, the transplantation of cancer, the observation of the influence of the nervous system on this or that natural process. In 1901, these experiments numbered 699. They cannot be compared with the same number of horses, cattle, or sheep mutilated by breeders and farmers; for these mutilations are done, some of them, without any anæsthetic. They cannot be compared with the same number of pheasants or rabbits badly wounded, but not killed, in sport; for the animals thus wounded receive no subsequent care, and, if they are in pain, nobody puts them out of it. But they may fairly be compared with the same number of pet animals that have undergone surgical operations at the hands of a skilled veterinary surgeon: only

with this difference, that many of them lose health, or suffer some disablement, and so die or are killed. But they must not be put to pain after the operation; nor must they be kept in pain. Whatever is done, must be done under anæsthesia: and there must be no *further* experiment, no observations made through the wound after the anæsthesia passes off. If morphia be used after ether, it is used in such a dose that the animal may be, like a man or woman, in danger of dying from an over-dose of the drug. On all these points the 1901 Report is decisive:—

"The operations are performed aseptically, and the healing of the wounds, as a rule, takes place without pain. If the antiseptic precautions fail, and suppuration occurs, the animal is required to be killed. It is generally essential for the success of these experiments that the wound should heal cleanly, and the surrounding parts remain in a healthy condition. Experiments involving the removal of important organs, and even of parts of the brain, are performed without causing pain to the animals; and after the section of a part of the nervous system, the resulting degenerative changes are painless.

"*In the event of a subsequent operation being necessary in an experiment performed under Certificate B, or B linked with EE, a condition is attached to the license requiring all operative procedures to be carried out under anæsthetics of sufficient power to prevent the animal feeling pain.*"

It is evident, from these Reports, that good

care is taken to ensure a minimum of pain. If sport were thus restricted, it would soon come to an end. The first time that a sportsman wounded a bird instead of killing it, he would be censured by a Government official; the second time, his gun-license would be revoked, a question would be asked about him in Parliament, and he would be held up to execration in the daily papers, for the slow, deliberate torture of helpless animals. He could plead, in excuse, only his right to please himself and his friends in his own way, and his intention to inflict, for his own pleasure, not torture, but only death. Experiments on animals have this excuse, that they are necessary not only for science but also in practice. In physiology, and in pathology, and in the prevention and the cure of disease, and in the operations of surgery, they have helped to save human lives literally in thousands and tens of thousands. Admit, that some of them involve pain, some have no direct bearing on practice, some fail, or are misinterpreted: there remains a whole legion of ourselves, rescued from disease and death, a multitude past all reckoning and ever increasing.

It might be worth the trouble, to collect and expose some of the false statements published by the opponents of all experiments on animals; but the task would be endless. This book is concerned only with the results that have been obtained by the help of these experiments, and with the Act relating to them. It was decided, and with authority, that it should be written for

general reading, should be published without reserve, and should not be anonymous. To write a "medical book" for general reading is hazardous work—*Utcunque jam jacta est alea: spes mea in amore veritatis et candore doctorum animorum.*

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